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«A COMPARATIVE PHARMACOLOGICAL STUDY OF THE EFFECTS OF NEUROLEPTICS DURING PREGNANCY AND THE PERINATAL PERIOD» (EXPERIMENTAL STUDIES)

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A B S T R A C T

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GENERAL DESCRIPTION OF THE WORK

Relevance and degree of processing of the topic. The mental health of an individual is one of the most significant factors that determine person's position in society and their ability to carry out normal life activities. In general, mental health refers to the satisfactory condition of a person to effectively utilize his potential, to cope with the stresses of daily life, to work productively and to contribute to society. In accordance with the World Health Organization (WHO), one out of four people worldwide suffer from psychological or neurological disorders at some point in their lives[1]. The stress people experience during their lives plays a significant role in the development of these disorders. At a young age, mental disorders such as depression, schizophrenia, eating disorders, and excessive use of harmful substances are more prevalent. Around 10-15% of young people with mental illnesses seek the assistance of mental health professionals in order to return to a normal life. Complications of mental disorders during family planning and pregnancy are also observed in such young people[2]. The fact that mental illnesses occur more frequently during the reproductive age of women and men, as well as the fact that there is little or no information regarding the effect of antipsychotic drugs prescribed for the purpose of treatment on this function in scientific sources, has prompted scientists and researchers to pay increased attention to this issue [3,4].

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[1] Ganiyev, M.M. Modern ideas about the mechanism of action of antipsychotic substances./ M.M. Ganiyev, M.F. Rustamova. // "Health" Scientific and practical magazine - 2019 - №2 p. 23-30.

[2] Мельников, В.А. Проблемы репродуктивного здоровья супружеских пар в современных условиях/Мельников В.А., Стулова С.В., Ермолаева Е.В. // Фундаментальные исследования.Москва, 2011, №10 (1), С.118-121.

[3] Маляров, С.А. Побочные реакции антипсихотических средств / С.А. Маляров, М.И. Добрянская // NeuroNews: психоневрология и нейропсихиатрия. – 2010. - №1 (20), С. 385-387.

[4] Altynbekov, K. S. Atypical antipsychotics: features modern pharmacotherapy (Review based on literature) // Proceedings of the 6th European Conference on Biology and Medical Sciences (June 10, 2015). «East West» Association for Advanced Studies and Higher Education GmbH. – Vienna, 2015. – P. 21–27.

In the opinion of several researchers during pregnancy, 10% to 79.3% of women have mild mental disorders, which may cause complications during pregnancy and childbirth, end the pregnancy with complications, and result in children born with defects[5,6,7]. Analysis of literature data, lack of sufficient fundamental scientific research in this direction, the presence of different and conflicting scientific opinions in the literature, the growth dynamics of mental pathologies, especially during the reproductive age, the large number of additional effects that appear during neuroleptherapy makes it necessary to study and investigate the effects of neuroleptics on the concentration of sex hormones, the course of pregnancy, and the prenatal and early postnatal development periods of the offspring.

As a result of the relevance of this issue, current research is focused on a comparative pharmacological study of how neuroleptherapy affects pregnancy and postnatal development in an experiment, in addition to the prenatal phase and early postnatal phase of the offspring.

The purpose and objectives of the research: A classical representative of the group of typical antipsychotic drugs – haloperidol, a butyrophenone derivative, and a potentially active representative of the group of atypical neuroleptics - a dibenzodiazepine derivative, clozapine, against the background of chronic administration, it consists of a comparative study of the effect on the concentration of reproductive hormones of white rats of both sexes, as well as the

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[5] Павлова,Л.К. Ипохондрические ремиссии при шизофрении (клиника, типологическая дифференциация, терапия). // Дисс. канд. мед. наук. Москва. 2017. -166 с.

[6] Серов, В.Н., Сухих, Г.Т., ред. Рациональная фармакотерапия в акушерстве, гинекологии и неонатологии: //Руководство для практических врачей. 2-е изд., испр. и доп. в 2 т. Т 1 Акушерство, неонатология М.: Литтерра; 2016. 784с.-с.201-230.

[7] Шер, С.А. Тератогенных воздействие лекарственных средств на организм будущего ребенка на этапе внутриутробного развития // Педиатрическая фармакология. Москва, 2014, Т.7, №6(8), С.57-59.

occurrence and course of pregnancy in rats, and the effect on the prenatal and early postnatal development periods of the offspring.

The following actions have been taken in order to achieve the set outcome:

1. A comparative study of the effects of clozapine and haloperidol on behavioral parameters of white rats.

2. A comparative study of the effects of haloperidol and clozapine administration to male white rats for a period of 21 days on the amount of lipid peroxide products (LPO) in different brain structures (hypothalamus, striatum, frontal cortex).

3. A comparative study of the effects of haloperidol and clozapine administration for 21 days on the amount of biogenic monoamines (MA) in different brain structures of male white rats.

4. A comparative study of changes in the amount of sex hormones in the blood of white rats of both sexes against the background of chronic administration of haloperidol and clozapine.

5. A comparative study of the changes in the physical development of offspring after chronic administration of haloperidol and clozapine to female, male and both sexes of rats.

6. A comparative study of changes in the rate of formation of motor-sensory reflexes and behavioral parameters of offspring after chronic administration of haloperidol and clozapine to female, male and both sexes of rats.

Research methods: “Open field”, spectrophotometry, spectrofluorometry methods, tests for immunoenzyme analysis, visual observation methods were used in conducting the research.

The main provisions of the defense: The amount of LPO products increases in a dose-dependent manner in different structures of the brains of male white rats given haloperidol and clozapine for 21 days, while a statistical decrease is observed in the amount of MA. Compared to clozapine, these alterations are more pronounced against the background of chronic administration of the typical neuroleptic haloperidol.

1. The concentration of sex hormones (except for PL) in the blood of white rats of both sexes, prescribed haloperidol and clozapi-

ne for 21 days, is statistically reduced. The effect of clozapine on these parameters is significantly lower than that of haloperidol.

2. Serious quantitative and qualitative changes were observed in the health and lethality indicators of the pups born from them, as well as in different gender, quantitative composition and physical development, against the background of 21-day administration of haloperidol and clozapine to female, male and both sexes. In a cross-comparison, these alterations, which were statistically deepened in a dose-dependent manner, were more pronounced in the offspring of haloperidol-treated rats.

3. A significant change observed in the rate of formation of behavioral parameters and motor-sensory reactions of offspring during the initial postnatal development period after the administration of haloperidol and clozapine to female, male and both sexes for 21 days against the background of clozapine administration, compared to the pups of the group of rats receiving haloperidol, it is manifested in a weaker intensity.

The scientific novelty of the research: This is the first complete comparison of the effects of haloperidol and clozapine on behavioral parameters, LPO products in brain structures, MA, the amount of sex hormones in the blood, as well as the number of pups born, and their physical development were comprehensively compared. Research findings indicate that haloperidol attenuates behavioral parameters in a dose-dependent manner more significantly than clozapine. While the amount of LPO products in brain structures is within the norm against the background of clozapine, it increases during chronic halo-peridol administration. During chronic administration of neuroleptics, a decrease in the amount of MA is observed. The study of the effect of both drugs on the amount of sex hormones proves that haloperidol reduces the amount of hormones in a dose-dependent manner (except PL) compared to clozapine. Additionally, haloperidol has a more negative impact on the number of offspring born, physical development, compared to clozapine. Increasing the dose of neuroleptics has a more negative effect on these processes.

The theoretical and practical significance of the research: The increase in demand for neuroleptics in the 21st century is due to the fact that people suffering from mental disorders are mostly of reproductive age. Taking these substances by any of the couples in the reproductive age causes serious problems in the control mechanisms and monitoring of pregnancy, especially during unplanned pregnancies. From this perspective, the occurrence and course of pregnancy against the background of 21-day prescription of haloperidol and clozapine, the experimental evidence of the effect on the defective development of the fetus, the confirmation of the negative effect of the group of neuroleptics on the reproductive function, are of special importance for practical medicine.

According to the results of the research it is very significant as a primary source in the direction of discovering the causes of the negative effect of chronic administration of haloperidol or clozapine on the reproductive system and developing an experimental model for eliminating the harmful effects and preparing clinical protocols.

From a clinical perspective, the conducted studies allow one or both of the couples chronically taking antipsychotic substances to have preliminary information about pregnancy and fetal pathologies that may occur during planned pregnancies and to take preventive measures to prevent it. The obtained results may also serve as an auxiliary tool during the planning of gynecological control of pregnant women who regularly take antipsychotic drugs from the group of neuroleptics due to necessity. The results of the conducted scientific research can be included in the teaching process of pharmacology, and can be used as a primary reference source when preparing textbooks, teaching aids, methodical work and scientific articles.

Approbation and application: Separate fragments of the dissertation work in the materials of the scientific conference dedicated to the 75th anniversary of the birth of Dr. Azam Aghayev Tayyar, Public health and healthcare volume VI, Baku-2019, in the materials of the International Scientific-Practical Conference on "Modern Problems of Neurosurgery" dedicated to the 50th anniversary of the establishment of the Department of Neurosurgery of the Azerbaijan Medical University, May 11-12, 2019, Baku-2019, International

scientific-practical conference, Science and education in the XXI century, Russia, Tambov, July 31, 2020, Part 1, Tambov 2020, edited.

The name of the organization where the dissertation work was performed:

The topic of the dissertation work is included in the scientific work plan of the Department of Pharmacology of AMU (State registration number №01114090, UOT:61.577.1). Scientific researches on relevant sections were carried out in the pharmacology department of AMU and the Scientific Research Center.

The scope and structure of the dissertation work.

The dissertation is printed on a hard copy on 173 pages (232.757 characters in total) and consists of an introduction (10.914 characters), a literature review (46806 characters), research materials and methods (13.683 points), 2 chapters from personal research (III chapter-52.568 points, IV chapter-49.085 points), conclusion (50.875 points), the results (3.085 points), practical recommendations (1.591 points), list of literature (43.585 points).

The dissertation work is illustrated with 19 tables and 9 pictures. The bibliography includes 260 sources, of which 24 are written in Azerbaijani, 114 are in Russian, and 122 are the works of scientists from other countries.

The materials and methods of the study.

Researches were carried out on 486 white healthy rats of both sexes, weighing 180-220 grams, kept under normal conditions in a vivarium. Doses of 0.5, 3 mg/kg of haloperidol and 10, 20 mg/kg of clozapine were used in the studies[8]. The animals of the control group were injected intraperitoneally with a physiological solution of 0.2

[8] Асметов, В.Я., Ганиев, М.М., Гасымова, Г.Н., Меликова, Н.В., Багирова, Н.В. Определение продуктов ПОЛ под действием галоперидола на фоне введения верапамила, пирацетама и мексидола в разных структурах головного мозга в острых опытах у крыс.// «Medical drugs for humans. Modern issues of pharmacotherapy and prescription of medicine» Materials of the V International Scientific and Practical Conference, 11-12 March 2021 Kharkiv, p. 205-208.

ml per 100 g of weight. For neurochemical studies, 30 rats were decapitated and the relevant brain structures were separated and examined.

The effects of haloperidol and clozapine on behavioral parameters were studied in the first group based on the dosage.

In male white rats included in the second and third groups, the amount of LPO products and MA in various structures of the brain was determined against the background of 21-day administration of haloperidol and clozapine.

In the fourth group, the change in the concentration of reproductive hormones was studied against the background of chronic administration of haloperidol and clozapine to male and female rats.

In the fifth group, changes in physical development and behavioral parameters during the early postnatal development period of the newborn generation against the background of chronic administration of neuroleptics to females, males and both sexes were studied.

During the determination of behavioral parameters of white rats, the "Open field" method, which is a classic and informative examination method, was used (M.M.Ganiyev, 1985).

Spectrophotometry (SF-16, Russian Federation) method was used to determine the amount of LPO products and MA in the homogenate prepared from various structures of the brain.

The concentration of sex hormones was performed using tests for enzyme immunoassays (Pishtaz, IR Iran).

The occurrence of pregnancy in female white rats was determined by the determination of spermatozoa in a smear taken from the uterus, the changes in physical activity and parameters during pregnancy, the physical development and defects in the early postnatal development periods of newborn pups were carried out against the background of visual observation using appropriate motor methods ("Open field", "Passive Protection from Conditional Reflexes").

The integrity and statistical analysis of the obtained results was conducted by comparing the relevant groups, using parametric (T-Student) and non-parametric (Wilcoxon-Manney-Whitney) criteria. All calculations were performed with the computer program EXCEL-2010. The results are reflected in tables and figures.

THE RESULTS AND DISCUSSION OF THE STUDY

The investigation of how long-term treatment of haloperidol and clozapine affects the behavioral characteristics of white rats as well as the amounts of LPO products, monoamines, and reproductive hormone concentrations in different brain areas

The study of behavioral parameters involved the use of haloperidol (0.5 and 3 mg/kg) and clozapine (10 and 20 mg/kg). Haloperidol at a dose of 0.5 mg/kg reduced locomotor activity by 50.1%, examination activity by 50.9%, vertical activity by 64.7%, grooming by 50.8% and defecation by 44.9%, while at a dose of 3 mg/kg, all parameters of behavior were more prominently attenuated. Clozapine at a dose of 10 mg/kg decreased motor activity by 51.9%, examination activity by 90.1%, vertical activity by 84.1%, grooming by 52.9%, and defecation decreased by 100%. All parameters of the behavior were statistically significantly more relaxed under the influence of 20 mg/kg clozapine. Haloperidol dose-dependently more significantly attenuated behavioral parameters than clozapine. This relaxation is due to the relaxing effect of drugs on the dopaminergic system[9].

When studying whether the studied neuroleptics have a pro- or antioxidant effect, it was found that while haloperidol at a dose of 0.5mg/kg increased the amount of DK in the hypothalamus by 28.4%, the amount of HP by 23.1%, the amount of MDA by 33.7% $p<0.01$, while the effect of 3mg/kg haloperidol increased the amount of DK by 2.4 times, the amount of HP by 93.1% and the amount of MDA by 2.5 times. While the amount of DK increased by 44.6%, HP content by 31.9%, MDA content by 32.4% $p<0.01$ under the influence of 0.5 mg/kg haloperidol in the frontal cortex, under the influence of 3 mg/kg haloperidol, the amount of DK increased by 2.4 times, the amount of HP by 99.3%, and the amount of MDA by 2.2 times.

While the amount of DK increased by 27.8%, the amount of HP by 24.3%, and the amount of MDA by 21.9% $p<0.01$ under the

[9] Reynolds, G.P. Beyond the dofamine hypothesis: The neurochemical pathology of schizophrenia. Br. J. Psychiatry, 1989; P.155-305.

influence of 0.5 mg/kg haloperidol in the striatum, due to the effect of 3 mg/kg haloperidol, the amount of DK increased by 2.8 times, the amount of HP by 2 times, and the amount of MDA by 2.1 times. While clozapine increased the amount of DK in the hypothalamus by 5.4%, 16.3% at doses of 10 and 20 mg/kg, it reduced the amount of HP and MDA in a dose-dependent manner. It increased the amount of DK in the frontal cortex by 10.9%, 18.2% $p<0.01$. There was almost no change in the amount of HP, in contrast, a dose-dependent decrease in the amount of MDA was observed. While the amount of DK increased in the striated body, a decrease was observed in the amount of HP, and almost no change was observed in the amount of MDA. According to our results, the idea that haloperidol has prooxidant properties and clozapine has antioxidant properties coincides with the results of other authors[10,11].

When studying the amount of MA, it was found that due to the effect of haloperidol at a dose of 0.5 mg/kg, the amount of serotonin in the hypothalamus decreased by 30.1%, in striated body by 47% and in the frontal cortex by 29%, and against the background of the chronic administration of a dose of 3 mg/kg, the amount of serotonin in the hypothalamus decreased by 51.7%, in the striatum by 58.7% and in the frontal cortex by 43%. While this indicator decreased by 9% in the hypothalamus, by 11.2% in the striatum, by 12.9% in the frontal cortex against the background of chronic administration of clozapine at a dose of 10 mg/kg, against the background of chronic administration of 20 mg/kg clozapine, this indicator decreased by 11.8% in the hypothalamus, 16.4% in the striatum, and 16% in the frontal cortex.

While the amount of NE decreased by 34.5% in the hypothalamus, 54.8% in the striatum, and 29.8% in the frontal cortex against

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[10] Алфимов П. В. Метаболический синдром у больных шизофренией (обзор литературы)/ П.В.Алфимов, П.В.Рывкин, М.Я.Ладыженский, С.Н.Мосолов // Современная терапия психических расстройств. - 2014. - №3. - С. 8-14.

[11] Attard A. Comparative effectiveness of atypical antipsychotics in schizophrenia: what have real-world trials taught us? / A. Attard, D. M. Taylor // CNS Drugs. 2016. - Vol. 26(6). - P. 491-508.

the background of chronic administration of haloperidol at a dose of 0.5 mg/kg, against the background of chronic administration at a dose of 3 mg/kg, the decrease in the amount of NE in the hypothalamus became more acute and reached 60.9%. In the striatum and frontal cortex, as a result of the chronic determination of the studied dose of haloperidol, a statistically significant decrease in the activity of the NE-ergic system occurs.

While the amount of neurotransmitter decreased by 19.8% in the hypothalamus, 13.9% in the striatum and 15.6% in the frontal cortex against the background of chronic administration of clozapine at a dose of 10 mg/kg, under the influence of 20 mg/kg clozapine, the amount of norepinephrine in the hypothalamus decreased by 21.7%, in the striatum by 17.8%, and in the frontal cortex by 18.1%. Against the background of dose-dependent chronic administration of haloperidol and clozapine, the amount of DA decreases as reliably as other MA. Against the background of chronic administration of haloperidol at a dose of 0.5 mg/kg, the amount of DA decreased by 31.7% in the striatum, and at a dose of 3 mg/kg, the amount of dopamine decreased by 59.5% in the hypothalamus, 66.7% in the striatum, and 63.2% in the frontal cortex. It is clear from the obtained results that clozapine dose-dependently decreased the amount of MA in all three structures with small numbers compared to both doses of haloperidol. The results are shown in figure 1.

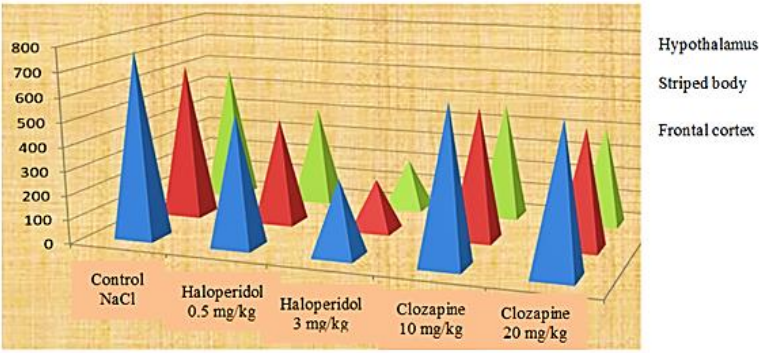

Figure 1. Effects of haloperidol and clozapine on the amount of dopamine in brain structures of male white rats

Against the background of chronic administration of the studied antipsychotic drugs, it can be explained as the acceleration of the breakdown of MAs due to the blockade of the receptors to which MAs bind and, therefore, their amount decreases in the structures of the brain[12,13].

In the studies, we studied changes in the amount of sex hormones (Tu, Ts, FSH, LH, PL, PG, ER, ED) against the background of chronic administration of haloperidol and clozapine to male and female animals. Against the background of chronic administration of haloperidol at a dose of 0.5 mg/kg to male animals, the concentration of Tu hormone decreased by 6.8%, Ts hormone 13.9%, FSH 24.1% (of which the indicator of Ts hormone was changed to invalid), the concentration of LH decreased by 49%, the concentration of PL increased by 33.3%, the hardness of PG by 74.6%, the hardness of ER by 77%, and the concentration of ED decreased by 97% statistically.

Against the background of the chronic administration of haloperidol at a dose of 3 mg/kg, these indicators were statistically significantly reduced. Against the background of chronic dose-dependent administration of clozapine to male animals, concentrations of Tu, Ts, PL (with exception), FSH, LH, PG, ER, ED hormones in blood plasma significantly decreased. Against the background of chronic administration of clozapine at a dose of 10 mg/kg, the concentration of the hormone Tu decreased by 6.4%, the concentration of Ts by 5%, the concentration of FSH by 31.1%, the concentration of LH by 44.5%, the amount of PG by 45.5%, the amount of ER by 65.8%, the amount of ED decreased by 96.3%, and the amount of PL increased by 14.2%. During the chronic administration of 20 mg/kg of clozapine, the concentration of Tu decreased by 6.1%, the density of Ts by 19.8%, the density of FSH by 20.7%, the density of LH by 48.7%,

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[12] De Hert, M. Do antipsychotic medications reduce or increase mortality in schizophrenia. A critical appraisal of the FIN-11 study. / M. De Hert, C.U. Correll, D.Cohen // Schizophr Res., 2016, vol. 117 (1), P. 68-74.

[13] Chan, J. Combination therapy with non – clozapine atypical antipsychotic medication: a review of current evidence. / J.Chan, M.Swettinq // J.Psychofarmacology. 2017, 21 (6), P. 657-664.

the density of PG by 48.59%, the density of ER by 31.7%, the concentration of ED decreased by 96.7%, and the concentration of PL increased by 27.12%. It is known from the results of the research that the concentrations of sex hormones in male animals are subject to change due to the effect of prescribed drugs. Haloperidol dose-dependently reduced the concentration of hormones in the blood of male animals more than clozapine.

When studying the changes in the concentration of sex hormones (Tu, Ts, FH, LH, PL, PG, ER, ED) of female animals against the background of chronic administration of haloperidol and clozapine in a dose-dependent manner, it was found that under the effect of 0.5 mg/kg dose of haloperidol, the concentration of Tu hormone decreased by 19.1%, the density of Ts hormone by 31.7%, the density of FSH by 37.8%, the density of LH by 51%, the density of PG by 49.6%, the density of ER by 52.4%, the concentration of ED decreased by 38%, and the concentration of PL increased by 37%. Against the background of chronic administration of a dose of 3 mg/kg of haloperidol, the concentration of Tu hormone in the blood of female animals decreased by 38.1%, the density of Ts hormone by 46.9%, the density of FSH by 48.2%, the density of LH by 63.7%, the density of PG by 56.5%, the density of ER by 73%, the concentration of ED decreased by 78.2%, while the amount of PL increased by 78.2%.

Clozapine at a dose of 10 mg/kg in the background of chronic administration to female white rats decreased the concentration of Tu hormone in the blood by 14.3%, the concentration of Ts hormone by 14%, the concentration of FSH by 22.2%, the concentration of LH by 62.8%, the concentration of PG by 42.2%, the concentration of ER by 40.5%, the concentration of ED by 28.2%, and increased the concentration of PL by 11.3%. These changes were partially exacerbated by clozapine at a dose of 20 mg/kg. These impairments are relative compared to the dose-dependent impairments produced by haloperidol.

The obtained results of the conducted studies are given in tables 1.

Table 1.

The effect of chronic administration of haloperidol and clozapine on the concentration of sex hormones in the blood of female white rats

M±m; n = 6

№	Groups	Tu(nmol/l)	Ts(pq/ml)	FSH(ME/ml)	LH(ME/ml)
1	Intact	0,21±0,03	0,79±0,04	1,58±0,12	1,72±0,03
2	Haloperidol 0,5mg/kg P %	0,17±0,01 > -19,1	0,54±0,03 <0,05 -31,7	1,00±0,024 <0,05 -37,8	0,73±0,02 <0,001 -51
3	Haloperidol 3mg/kg P %	0,13±0,02 <0,05 -38,1	0,42±0,02 >0,61 -46,9	0,82±0,03 >0,01 -48,2	0,59±0,06 <0,001 -63,7
4	Clozapine 10mg/kg P %	0,18±0,02 >0,05 -14,3	0,68±0,06 <0,001 -14	1,23±0,08 <0,05 -22,2	0,64±0,02 <0,001 -62,8
5	Clozapine 20mg/kg P %	0,15±0,04 >0,05 -28,6	0,63±0,02 <0,001 -20,3	1,19±0,07 <0,05 -24,7	0,62±0,01 <0,001 -64

Continuation of table 1

№	Groups	PL(ME/ml)	PG(nmol/l)	ER(nq/l)	ED(pq/ml)
1	Intact	240,4±6,3	14,2±1,06	1,88±0,09	14,28±1,05
2	Haloperidol 0,5mg/kg P %	329,9±7,2 >0,01 37	7,14±1,08 <0,001 -49,6	0,82±0,04 <0,05 -52,4	8,86±0,03 <0,001 -38
3	Haloperidol 3mg/kg P %	420,7±6,8 >0,01 75	6,18±0,80 <0,001 -56,5	0,51±0,02 <0,05 -73	3,12±0,09 <0,05 -78,2
4	Clozapine 10mg/kg P %	271,8±5,4 <0,001 11,3	8,21±0,84 >0,01 -42,2	1,12±0,06 <0,05 -40,5	10,26±0,8 <0,01 -28,2
5	Clozapine 20mg/kg P %	297,6±5,4 <0,001 23,7	7,99±0,76 >0,01 -43,8	1,06±0,04 <0,05 -43,7	9,19±0,5 <0,01 -35,7

p - coefficient of integrity

From the obtained results, we conclude that long-term administration of haloperidol reduces the amount of MA in different structures of the brain. A decrease in the amount of MA leads to a change in the concentration of many neuropeptides that play an significant role in the functioning of the reproductive system. It has been proved that

there is a connection between these reductions and a decrease in the concentration of LH [14]. Chronic intake of antipsychotic drugs caused not only a decrease in the concentration of LH, but also a decrease in the concentration of all sex hormones, except for PL. These reductions have been confirmed again in our research.

A comparative study of the changes in the development of the newborn offspring in the antenatal and postnatal periods against the background of chronic administration of haloperidol and clozapine

When studying the effect of the investigated medicinal substances on the duration of pregnancy in female rats, it was found that against the backdrop of chronic administration of a dose of 0.5 mg/kg of haloperidol, the duration of pregnancy was 1.75 days, as a result of the effect of a dose of 3 mg/kg, 3.45 days, the effect of clozapine at a dose of 10 mg/kg was shortened by 1.25 days, and by 20 mg/kg by 1.75 days. When studying the effect of drugs on body weight, it was found that it was statistically significantly reduced 8.7% of pre-natal weight in rats administered haloperidol at a dose of 0.5 mg/kg, 12% of the effect of haloperidol at a dose of 3 mg/kg, and by 5.8% from the effect of clozapine at a dose of 10 mg/kg, by 7.3% from the effect of clozapine at a dose of 20 mg/kg. Against the background of chronic administration of both drugs in a dose-dependent manner, noticeable deviations in the behavior of pregnant rats were visually observed during the course of pregnancy.

It was recorded that the mucous membranes of pregnant rats were clean, and the outer coat was not smooth and dense. It was observed that pregnant females in all research groups did not build straw nests to place their young 2-3 days before birth. On the other hand, it was determined that the important difference in the course and character of the birth process in pregnant rats was exceptional.

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In our experiments, the difference and changes between the body weight of pregnant rats in the last days of pregnancy and the weight after birth were evaluated. A decrease in the tendency of females to care for newborn cubs during the lactation period has been recorded. Attention has been drawn to the decrease in cases of rats protecting cubs from the environment and covering them, as well as the increase in actions such as biting and injuring their own cubs. In the group given 0.5mg/kg dose of haloperidol, the postnatal weight of animals was reduced by 3%, while the postnatal weight of animals given the dose of 3mg/kg was reduced by 12%, a 5.2% increase was observed from the effect of clozapine at a dose of 10 mg/kg, and a 7.9% increase from the effect of clozapine at a dose of 20 mg/kg. This is the result of the other direction effect of clozapine compared to haloperidol. The obtained results have been confirmed in other studies [15,16].

In the postnatal period, many physical defects or anomalies are found in the newborn offspring. Disturbance of the symmetry of the anatomical structures of the face and skull, including the jaw, palate, nasal cavity, and eye sockets, and stillbirths of cubs were found. The weight of pups decreased by 24.6% during the chronic administration of 0.5mg/kg dose of haloperidol, and by 41.5% during the administration of 3mg/kg dose ($p<0.05$). Against the background of 10mg/kg dose of clozapine, the decrease in body weight of pups was 20%, and when 20mg/kg dose was determined, it was 22.2%.

A decrease in the number of pups born in the study groups was also observed. The total number of pups born against the background of chronic administration of 0.5 mg/kg dose of haloperidol decreased by 33.3%, and the number of pups in the 3mg/kg group decreased by 61.1%, the total number of pups born at a dose of 10mg/kg of clozapine decreased by 13% and the number of pups in the 20 mg/kg group decreased by 17.6%.

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In the studies, the course and nature of labor in female rats were dramatically different against the background of chronic administration of haloperidol 0.5 mg/kg, 3 mg/kg and clozapine 10 and 20 mg/kg. Disturbances during chronic dose-dependent administration of haloperidol were more serious compared to clozapine. Visual observation after birth revealed the presence of anomalies in the external appearance of some of the offspring in all research groups.

Compared to the control group, stillbirths were observed due to the dose-dependent effect of both studied drugs. The number of dead pups was 8 (11.7%) under the influence of a dose of 0.5 mg/kg of haloperidol, and 10 (19.6%) under the influence of a dose of 3 mg/kg and the number of dead pups was 2 (2.8%) due to the dose of clozapine 10 mg/kg, and 3 (4.5%) due to the dose of clozapine 20 mg/kg.

The sex characteristics of the offspring were also studied against the background of chronic administration of both studied doses of haloperidol and clozapine to females. While the number of male and female offspring in the offspring from females in the control group was 44, the number of male pups in the generation born against the background of chronic administration of 0.5 mg/kg dose of haloperidol to females was 33 (55.5%), and the number of female pups was 27 (45.5%), during chronic administration of 3 mg/kg dose, the number of male pups was 20 (48.7%), and the number of female pups was 21 (51.3%). It can be concluded from this that the drugs we prescribed to female animals did not significantly affect the number of sexes of the newly born generation, except for slight differences. Against the background of chronic administration of 10mg/kg dose of clozapine, the number of male pups was 37 (53.6%), the number of female pups was 32 (46.4), against the background of setting a dose of 20 mg/kg, the number of male pups was 39 (59.1%), and the number of female pups was 27 (40.9%).

From the other developmental indicators of the offspring born on the background of chronic administration of research drugs to females, it was found that the rate of opening of the ear canal was 22.2% slower than the effect of the 0.5 mg/kg dose of haloperidol, and 55.6% later than the effect of the 3 mg/kg dose and 5.6% later

than the effect of the 10 mg/kg dose of clozapine, and 16.6% later than the 20 mg/kg dose. The criteria of physical development that we mentioned were more pronounced due to the dose-dependent effect of haloperidol compared to clozapine. The formation of the primary coat of the offspring is significantly delayed against the background of the appointment of both doses of the studied drugs to females. In the control group, hair coat formation was 5.4±0.24 days, while in the haloperidol 0.5mg/kg dose group it was 6.2±0.24 days and 6.6±0.24 days in the 3mg/kg dose group, and in the clozapine 10 mg/kg dose group it was 5.9±0.24 days, and 6.0±0.31 days in the 20 mg/kg dose group. This shows that it is caused by the additional teratogenic effects of drugs during chronic administration[17,18,19]. At the same time, there is a delay in the formation of the reverse geotaxis reaction. The formation of the reverse geotaxis reaction of the new generation was 6.8±0.37 in the control group, 7.2±0.32 in the background of the 0.5 mg/kg dose of haloperidol, and 7.3±0.2 in the background of the 3 mg/kg dose, and 7.2±0.24 in the background of setting the dose of 10 mg/kg of clozapine, and 7.4±0.31 in the background of setting the dose of 20 mg/kg.

Although there was a visual increase in the opening of the reproductive tract in female chicks and the increase in the duration of seeding in male chicks, this was not statistically significant ($p>0.05$).

The number of pups born with anomalies was found in 2 pups in the group receiving 0.5 mg/kg dose of haloperidol, 3 pups in the group receiving 3 mg/kg dose, and 1 pup in the groups receiving 10 and 20 mg/kg doses of clozapine. Significant changes in the course of pregnancy and visual abnormalities in the birth process were

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recorded in female rats prescribed research drugs. In some pups, the skull and facial skeleton were not symmetrical, limbs, tail, eye sockets, nostrils, mouth gap were abnormal.

During the chronic administration of the studied drugs to males, the course of pregnancy and the toxic effect on the offspring were more prominent in females mated with them.

When we pay attention to the number of newly born offspring, we notice that the number of pups given birth to 0.5 mg/kg dose of haloperidol for males was 22 pups, and 28 pups were born to 3mg/kg dose, and 8 pups given birth to the 10 mg/kg dose of clozapine, and 10 pups were born in the 20 mg/kg group. A more significant statistically significant reduction was observed in the number of progeny from males exposed to the 3 mg/kg dose of haloperidol. This is the main manifestation of the dose-dependent effect of research drugs on the number and weight of the newly born offspring.

As can be seen, the difference in the weight and number of pups born on the background of the administration of research drugs to females, in contrast to the pups born on the background of administration to males, leads to the opinion that the change in the direction of decrease in weight and number is related to the effect of the research preparations on the fetus in the womb and causes corresponding functional changes [20,21].

Differences in prenatal and antenatal quantitative parameters of pups born during the mating of healthy females and male rats exposed to the study drugs are the result of the strong effect of the respective study drugs on male germ cells [22,23].

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[22] Ikegami, K. Seasonal time measurement during reproduction / K, Ikegami, T, Yoshimura // J. Reprod. Dev. – 2013. – Vol. 59, No. 4. – P. 327-333.

[23] Walker, W.H. Testosterone signaling and the regulation of spermatogenesis / W.H. Walker // Spermatogenesis. 2015.Vol.1, № 2. P. 116-120.

The presence of anomalies in the pups born as a result of the mating of female and male rats prescribed research drugs was revealed. This is the result of the long-term administration of the studied drugs to men, which has a negative effect on the offspring. As can be seen from the results, the number of pups born was significantly reduced, dead pups after birth were absent in the control group, but in the study group.

The birth rate of female pups has decreased across groups. The total number of female pups born on the background of chronic administration of 0.5 mg/kg dose of haloperidol to males was 30 pups, and 28 pups on the background of 3 mg/kg dose, and 35 pups on the background of 10 mg/kg dose of clozapine, and 34 pups on the background of 20 mg/kg dose.

From our research it was determined that chronic administration of haloperidol 0.5 mg/kg, 3 mg/kg, clozapine 10 mg/kg and 20 mg/kg to males showed undesirable effects on offspring, and it is dangerous in terms of fetal abnormality and prenatal development profile. This also revealed the fact that there is a change in the physical development of the pups against the background of chronic administration of the drugs.

Against the background of chronic administration of haloperidol 0.5mg/kg, 3mg/kg, clozapine 10mg/kg and 20mg/kg, the rate of ear canal opening in the corresponding group of pups was 1.8±0.2 days in the control group, and 2.3±0.2 days from the effect of haloperidol dose of 0.5mg/kg, 2.6±0.24 days from the effect of 3mg/kg dose, and clozapine was 1.8±0.2 days from the effect of 10mg/kg dose and 2.0±0.1 days from the effect of 20mg/kg dose ($p<0.001$).

While in the control group, the formation of primary plumage in the newly born generation was 5.4±0.24 days, and 6.4±0.24 days from the effect of a dose of 0.5 mg/kg of haloperidol, 6.9±0.37 days from the effect of a dose of 3 mg/kg, and 5.9±0.2 days after the 10mg/kg dose of clozapine and 6.1±0.3 days after the 20mg/kg dose.

While the formation of reverse geotaxis reaction was 6.8 days in the control group, 7.4±0.32 days from the effect of a dose of 0.5 mg/kg of haloperidol, 7.8±0.37 days from the effect of a dose of 3 mg/kg, 7.2±0.32 days from the effect of 10 mg/kg dose of clozapine,

and 7.3±0.29 days from the effect of 20 mg/kg dose. At the same time, against the background of dose-dependent chronic administration of these medicinal substances, the opening of the teeth, the opening of the eyes, the opening of the birth canal in female pups, and the prolongation of the period of seeding in male pups were statistically honestly recorded.

Regarding the number of stillborn babies, it was known that there were no stillborn pups in the 0.5 mg/kg haloperidol group, 3 in the 3 mg/kg group, and 10 and 20 mg/kg clozapine groups. Visual observation of the pups within 24-48 hours after birth revealed the fact that there was an anomaly in the appearance of the offspring in all research groups. The skull and facial skeleton were not symmetrical, the limbs, tail, eye sockets, nostrils, mouth cleft were abnormal.

Research has shown that haloperidol has more pronounced adverse effects on the offspring when given chronically to male rats than clozapine at doses of 0.5 mg/kg and 3 mg/kg and is dangerous in terms of fetal appearance and prenatal developmental profile.

When our research was conducted on pups obtained from white rats of both sexes against the background of chronic administration of the studied drugs, it was found that during the chronic administration of 0.5 mg/kg dose of haloperidol to both sexes, the number of live births decreased by 26.2%. That is, while the number of pups born alive in the control group was 88, the number of pups born alive was 65 under the influence of haloperidol 0.5 mg/kg, 63 under the influence of 3 mg/kg, and 82 and 78 under the influence of clozapine 10 and 20 mg/kg.

While the sex indicators of the pups born in the control group were equal, against the background of chronic administration of 0.5 mg/kg dose of haloperidol to both sexes, the number of male litters was 46.1%, and the number of female litters was 53.9%. The number of male litters of both sexes that received the 3 mg/kg dose of haloperidol was 50.8%, and the number of female litters was 49.2%. Although 51.2%; 48.8% of pups in animals that received clozapine at a dose of 10 mg/kg, 52.5% and 47.5% in pups that received a dose of 20 mg/kg, against both doses of haloperidol, the number of male and female offspring of both sexes was greater.

Against the background of chronic prescription of antipsychotic drugs, the opening of the ear canal in the new generation is delayed by days.

The rate of delay in the formation of primary hair cover was 22.2% in the group prescribed a dose of 0.5 mg/kg of haloperidol, and 31.5% in the group prescribed a dose of 3 mg/kg, and 11% in the group of perscribed a dose of 10 mg/kg of clozapine and 14.8% in the 20 mg/kg group.

A statistically significant delay was also recorded in the reverse geotaxis response. In rat pups of both sexes who received the studied drugs chronically, starting from the 28th day of the postnatal period, as a result of visual inspection, an increase in the weakening of the pace of opening of the pupal tract was observed, but this was determined to be statistically insignificant.

The analysis of the obtained results of the conducted studies proved the delay of some parameters of the postnatal development of the newly born generation, which were affected by the studied drugs in the mother's womb and during breastfeeding. Noticeable delay of physical development parameters such as opening of eyes and opening of teeth in the corresponding group of pups, opening of the uterus in female pups, and seeding in male pups attracted attention.

Ear canal opening in pups was delayed in animals given clozapine 10 and 20 mg/kg compared to 0.5 and 3 mg/kg haloperidol, and surface retardation in reverse geotaxis response. There was a trend of delay in the formation of primary hair cover in pups of all groups. Other physical development parameters were identical to those of the control group and fixation was recorded.

According to the obtained results of the studies, we conclude that haloperidol causes a greater delay in some parameters of the postnatal development of the newborn offspring compared to clozapine in a dose-dependent manner.

During the dose-dependent administration of the investigated medicinal substances to both sexes, noticeable changes in the course of pregnancy and abnormal birth process were observed in rats. After the birth process, the visual observation of the pups for 24-48 hours revealed the fact that there was an anomaly in the appearance of the

offspring in all research groups. 3 and 4 pups were born with anomalies in both doses of haloperidol and 1 pup in both doses of clozapine, respectively. In pups with this anomaly, the skull and facial skeleton were not symmetrical, the limbs, tail, eye socket, nostrils, mouth cleft were abnormal. This gives reason to conclude that the studied medicinal substances have a strong terotogenic effect on the offspring.

Based on the study of the effect of medicinal substances on the reproductive function and developmental parameters of the new generation of rats, it was found that the administration of these medicinal substances before and during pregnancy is unacceptable. However, when we analyze the results of our studies, we conclude that clozapine can be used in life-threatening situations and desperate situations.

Thus, we come to the conclusion that the intake of haloperidol and clozapine by both sexes has the potential to have a toxic effect on the fetus, and they can be considered dangerous drugs for the new generation of both sexes.

In conclusion, the results of our research show that the effects of haloperidol and clozapine on the CNS of newborn pups in a dose-dependent manner are multidirectional and ambiguous. We believe that there are delays in motor activity in the newly born generation against the background of taking haloperidol and clozapine, and it can be said that postsynaptic mechanisms are based on this, and inhibitory processes in neuromediator systems are dominant.

CONCLUSION

1. At a postsynaptic dosage (0,5 and 3 mg/kg), haloperidol, a classic representative of neuroleptics, has a relaxing effect on behavioral parameters. Increasing the dosage of the drug is associated with the strengthening of the inhibitory effect on the motor parameters. In parallel experiments, the depressant effect of clozapine on locomotor activity, although statistically honest, is markedly inferior to that of haloperidol. Behavioral parameters are affected by neuroleptics in the same direction, but with different degrees of activity,

due to haloperidol's tropism on postsynaptic, and clozapine's, mainly on autoregulatory dopaminergic processes [1,4].

2. As a result of chronic administration of haloperidol and clozapine, significant changes in the amount of LPO products were observed in various brain structures (hypothalamus, striatum, and frontal cortex) of male white rats. While haloperidol at doses of 0.5 and 3 mg/kg caused a statistically significant increase in the amount of LPO products in all three brain structures, clozapine at doses of 10 and 20 mg/kg slightly increased the amount of DK from LPO products compared to the control group, but decreased the amount of HP and MDA. According to the comparative analysis of the results, haloperidol has prooxidant activity, while clozapine has antioxidant activity, depending on the dosage of use [5].

3. A statistical decrease in the amount of biogenic amines in brain structures is recorded during the chronic administration of haloperidol and clozapine. Depending on the dose of use, a stronger decrease in the amount of biogenic amines is observed against the background of long-term administration of haloperidol, a typical antipsychotic drug [3,6].

4. In the blood of white rats of both sexes, chronic administration of haloperidol and clozapine produced statistically significant changes in the concentration of sex hormones. Therefore, haloperidol dose-dependently reduces the amount of all studied sex hormones (except for PL, which increases the concentration of PL in the blood). Against the background of clozapine, there is a decrease in the amount of other sex hormones, except Tu, Ts, PL hormones [8, 10, 11].

5. Chronic administration of haloperidol and clozapine to female, male, and both sexes of rats caused significant physical developmental changes in their offspring. Both doses of haloperodol used shortened the duration of pregnancy more than both doses of clozapine used. Haloperidol decreased the pre- and post-partum weight of pregnant rats, whereas clozapine statistically significantly increased the post-partum weight. The postnatal weight of pups and the decrease in the number of pups, which occurred against the background

of chronic administration of both neuroleptics, were more observed against the background of haloperidol administration [2, 9].

6. Statistically significant changes in the rate of formation of motor-sensory reflexes and behavioral parameters of the pups born from them are observed against the background of chronic administration of haloperidol and clozapine to female, male and both sexes of rats. In pups born against the background of chronic administration of both neuroleptics, depending on the dose of use, there is an increase in the number of pups born with opening of the ear canal, reverse geotaxis reactions, delays in the formation of fur, anomalies and physical development defects. Abnormal and physical malformations are more common in pups born to rats of both sexes chronically receiving haloperidol [7].

PRACTICAL RECOMMENDATIONS

1. When prescribing antipsychotic medications to family planning men and women suffering from mental illness, it is necessary to take into account that they are likely to cause pregnancy and fetal pathologies and that such changes are based on the important role of changes in neuromediator processes, especially in the dopaminergic system and the amount of LPO products in brain structures.

2. It should be taken into account as a necessary practical recommendation that during family planning men and women who regularly take neuroleptics and suffer from mental illnesses, reduction of the concentration of sex hormones (except PL) of neurolepotherapy, in the experiment, the shortening of the duration of pregnancy, the lack of physical development of the fetus, intrauterine developmental defects, i.e., terotogenic effect, as well as intrauterine death, should be kept strictly under the supervision of a specialist.

3. From the point of view of unwanted side effects observed in experiments on pregnant women suffering from mental pathology, especially in case of pregnancy, the appointment of classical-typical representatives of the group of antipsychotic drugs should not be

considered appropriate, and in desperate situations, the use of atypical neuroleptics should be recommended.

4. For couples suffering from mental illness, planning a family, as well as during pregnancy, in cases where non-specific unwanted side effects observed in the experiment are suspected as a result of instrumental gynecological examinations, the use of medicinal substances from other, especially non-psychoactive, groups may be recommended for correction purposes.

The list of published scientific works on the topic of the dissertation

1. Rustamova M.F. Haloperidol and its pharmacological properties. // “Health” Scientific and practical magazine - 2017 - №1 p:187-191
2. Rustamova M.F. The role of folic acid during pregnancy. // “Modern achievements of Azerbaijani medicine” Scientific and practical journal - 2019 - №2 p:23-31
3. Rustamova M.F. A comparative study of the effects of haloperidol and clozapine on the amount of serotonin in different structures of the brain. // “Azerbaijan Medical Journal” - 2019 (special edition) p:178-179
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5. Rustamova M.F. Determination of changes in the amount of lipid peroxide products in white rats in different structures of the brain under the influence of neuroleptics. // “Journal of Azerbaijan Psychiatry” - 2019 - №1(33) p:118-127
6. Rustamova M.F. Effects of haloperidol and clozapine on the amount of norepinephrine and dopamine in brain structures of male rats. // “Health” Scientific and practical journal - 2019 - №3 p:111-116
7. Rustamova M.F. Changes in quantitative and anatomic parameters of progeny from males given haloperidol and clozapine. // “Public health and healthcare” Volume VI - 2019 p: 288-293

8. Ганиев М.М., Рустамова М.Ф. Экспериментальное изучение влияние нейролептиков на уровень половых гормонов в крови крыс. // « Международный научный журнал» Москва - 2019 - №2 стр: 91-96.

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LIST OF CONDITIONAL ABBREVIATIONS

AOMS	–	Antioxidant defense system
BMA	–	Biogenic monoamines
DA	–	Dopamine
ED	–	Estradiol
ER	–	Estrol
FSH	–	Folliclestimulating hormone
HHQS	–	Hypothalamus-pituitary-gonadal system
HP	–	Hydroperoxides
Hs	–	Hypothalamus
KA	–	Catecholamines
QRF	–	Gonodotropic releasing factor
LH	–	Luteinizing hormone
LPO	–	Lipid peroxidation
MA	–	Monoamines
MAO	–	Monoamine oxidase
MDA	–	Malondialdehyde
CNS	–	Central nervous system
NE	–	Norepinephrine
PL	–	Prolactin
FRO	–	Free radical oxidation
T	–	Testosterone
Ts	–	Free testosterone
Tu	–	Testosterone total
WHO	–	World health organization
5-HT	–	Serotonin

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