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ABSTRACT

Of the dissertation for the degree Doctor of Philosophy

NEW COMPLEX COMPOUND BASED ON PALLADIUM AND MEXIDOL AND ITS TOXICOLOGICAL AND PHARMACOLOGICAL STUDY

Speciality:	3209.01 – Pharmacology, clinical pharmacology
Field of science:	Biology
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GENERAL DESCRIPTION OF THE WORK

Relevance of the work. Drug intervention is necessary for the treatment of many diseases. The management of numerous diseases necessitates pharmacological intervention, where the primary criteria for pharmacological agents are not only efficacy but also safety. That is, the medications having the highest therapeutic efficacy while exhibiting the lowest toxicity are required. The search for such drugs is a critical issue in pharmaceutical and medical sciences.

The problem of identifying chemotherapeutic medicines with comparatively low levels of toxicity is particularly pressing. Given how these medications work on cancerous cells, there is a good chance that they will harm the body's healthy cells as well. Consequently, their adverse effects frequently limit chemotherapy treatment effectiveness and significantly impair the quality of life of the patients.

Platinum compounds are thought to be among the most potent medications in the chemotherapeutic treatment arsenal. However, despite their high effectiveness, these medications have substantial hepato-, nephro-, and neurotoxicity, which restricts their potential applications in medicine. As a result, contemporary research efforts have increasingly focused on investigating alternative compounds of other members of the platinum group metals. Among these alternative metal complexes, palladium-containing compounds have emerged as particularly promising candidates for further development and study. These palladium derivatives demonstrate a strongly pronounced antitumor effect while exhibiting markedly reduced overall toxicity to the body in whole[1]. Stable palladium complexes have been found to deliver palladium to cellular targets more selectively. Once there, they attach to[2]

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[1] Грехова, А.К. Сравнительные исследования генотоксичности нового ацидокомплекса палладия (II) и цисплатина в лимфоцитах крови человека in vitro / А.К. Грехова Л.Б Горбачева., Н.А Иванова. [и др.].// Биомедицинская химия, – 2013. Т. 59. № 1, – с. 107-114.

[2] Денисов, М.С. Глушков, В.А. Биологически активные комплексы палладия (II) и n-гетероциклических ароматических лигандов (обзор литературы): [Электронный ресурс] / Вестник Пермского Университета. Серия: Химия, 8(4), 388-411. – 2018. URL: https://doi.org/10.17072/2223-1838-2018-4-388-411.

specific intracellular structures of neoplasms, which stops the growth and metastasis of cancer cells[3].

A novel complex of palladium and mexidol (2-ethyl-6-methyl-3-hydroxypyridine ammonium tetrachloropalladate), commonly known as mexidazole, was synthesized at Research Centre of Azerbaijan Medical University. Mexidazole may show encouraging anticancer activity when used to treat oncological diseases. A study carried out under the direction of Professor Dr. Burak Tüzün, employing mathematical modeling, supported this premise[4]. Scientific evidence suggests that palladium might possibly have radioprotective qualities[5]. As a result, we believe it is most important to investigate the toxicity of this molecule, which will allow us to propose a novel chemical for investigation as an antitumor chemotherapeutic agent as well as a radioprotective agent to defend against the harmful effects of radiation.

Study objectives: To determine the acute, subchronic and chronic toxicity of mexidazole (Mex) in comparison with cisplatine (Cis) and to study experimentally its radioprotective activity in an experiment.

Research objectives:

1. To determine the acute toxicity of mexidazole:
   - To determine the LD_{50} of mexidazole in laboratory rodents (mice and rats) with separate determinations for each sex.

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[3] Ефименко, И.А., Чураков, А.В., Иванова, Н.А. [и др.] Некоторые аспекты биологической активности координационных соединений палладия, в книге // Третья Всероссийская научная конференция (с международным участием): «Успехи синтеза и комплексообразования» тезисы докладов, – Москва: – 21-25 апреля, – 2014, – с.17.

[4] Tüzün, B., Jafarova, R., Bagirov, I. Magerramova N. [et al.] Mathematical Modeling of the Biological Activity of a New Complex Compound Based on Palladium and Mexidol: [Electronic resource] / Journal of Biochemical Technology 14(1), 40-44. – March 17, 2023. URL:https://doi.org/10.51847/ksxuz54Cjf

[5] Ефименко, И.А. Первые полиядерные соединения палладия $[(C_5H_{12}NO)(PdCl_3)]n$ и $[(C_{10}H_{16}NO)_2(Pd2Cl_6)]$ с высокой противоопухолевой и радиопротекторной активностью / И.А.Ефименко, М.В.Филимонова, А.В.Чураков [и др.] // Координационная химия, – Москва: – 2020. т. 46, № 5, – с. 304-315.

- To determine the tolerable, toxic, and lethal doses of the test substance.
- To document the clinical picture of intoxication and determine the cause of death of animals.

2. To determine the subchronic toxicity of mexidazole:

3. To study the chronic toxicity of mexidazole in a comparative context with cisplatine:

- to determine the changes in blood composition including the formed elements as well as the levels of creatinine;
- to determine the changes in urine parameters, such as color, volume, density, and pH, as well as the presence of sediment, blood traces, bilirubin, urobilinogen, ketone bodies, protein, nitrites, glucose, leukocytes, creatinine;
- to determine the glomerular filtration rate (GFR);
- to identify the changes in behavioral responses of the animals.

4. To study the radioprotective properties of mexidazole.

Study methods:

1. The acute toxicity was determined using the Spearman-Karber method.
2. The subchronic toxicity determined using the Lim R.K. method.
3. The chronic toxicity was determined based on the results of blood and urine laboratory tests, macroscopic panel of internal organs, assessment of integral indicators and symptoms of neurotoxicity.
4. The radioprotective properties were determined using the "protection percentage" - the difference between the level of manifestation of the effect (the changes in the percentage content of the blood formed elements (hematology)) against the background of the administration of the studied compound and without it.

The main provisions of the dissertation submitted for defense:

1. Mexidazole is a substance that shows promise for medical research. According to the investigations, the hemato-,

nephro-, and neurotoxicity of acute, subchronic, and chronic cisplatine is substantially higher.

2. Mexidazole - this innovative compound shows notable radioprotective effects after a single, variable-intensity X-ray exposure. An increase in the compound's protective action is observed which is directly correlated with an increase in irradiation intensity.

Scientific novelty of the Study:

For the first time:

- LD_{50} values for male and female mice and rats were established during in the course of the studies to ascertain the acute toxicity of Mexidazole - novel complex.
- The interior organs of the chest and abdominal cavities were examined under a microscope, and alterations that were incompatible with life were discovered. The greatest damages were discovered in the liver and kidneys.
- The cumulation coefficient of Mexidazole, C_c, was determined to be less than 1 when the accumulation was examined using the Lym technique, indicating that it accumulates in the bodies of animals.
- It was established that compared to the administration of cisplatine, mexidazole causes fewer abnormalities of the blood's composition and index of produced elements. There is a discernible association between a few indicators: WBC (10^9/L) – LYM (10^9/L): $\rho=0.83$; $p<0.01$ (significant positive correlation); LYM (10^9/L) – MID (10^9/L): $\rho=0.578$; $p<0.05$ (significant positive correlation); MCV (fh) – MCH (pg): $\rho=0.661$; $p<0.05$ (significant positive correlation); RDW-SD(fl) – RDW-CV(%): $\rho=0.309$; $p>0.05$; PDW (%) – PCT (%): $\rho=-0.442$; $p>0.05$, indicating that these parameters are important for tracking the level of intoxication under the exposure to studied compounds.
- Mexidazole causes statistically much less liver and kidney damage than the reference medication, cisplatine, according to toxicological tests. This is supported by a noticeably reduced level of leukocytes, urobilinogen, bilirubin, proteins, and blood in the urine, and a lesser drop in GFR.

– Mexidazole's radioprotective qualities have been established. There is a clear relationship between the rise in irradiation intensity and the degree of the compound's protective effects.

Theoretical and practical significance of the study.

1. Mexidazole shows promise for usage in medicine as it is much less toxic than the comparison medication.
2. A new compound was synthesized which has radiprotective properties and based on preliminary data, may be a promising radioprotective agent.

The object and subject of the Study. The subject of the study was a new palladium and mexidazol complex compound. The study's objects were 130 white laboratory mice of both sexes with the weight 18-23 g and 510 white outbred rats weighing 185-276 g. Every animal in the experiment was housed under the same care and feeding guidelines, and all requirements of the 1986 Strasbourg "European Convention for the Protection of Vertebrate Animals used for Experimental and Other Purposes" (Strasbourg, 1986) were met.

Approbation and implementation of the study results. The main provisions of the dissertation have been presented at the following conferences: International Conference Process Management and Scientific Developments" Birmingham, United Kingdom (November 14, 2019), İmaməddin Nəsiminin 650 illik yubileyinə həsr olunmuş – Doktorantların və gənc tədqiqatçıların XXIII Respublika elmi konfransı (Bakı, 2019.), Azərbaycan Tibb Universitetinin 90 illik yubileyinə həsr olunmuş "TƏBABƏTIN AKTUAL PROBLEMLƏRİ-2020" mövzusunda beynalxalq elmi-praktik konqresin materialları, The XXI International Scientific Symposium «Science and Culture in the Modern World» (Stockholm/Sweden, 2021), 7th International Izmir Congress on medicine, nursing, midwifery, and health sciences (İzmir, 2025), and were discussed at Scientific Research Centre of Azerbaijan Medical University (2022; 2023).

The relation of the study to the most relevant scientific problems in medical science. The dissertation was a component of

the research theme plan of Scientific Research Center of the Azerbaijan Medical University Republican Program "Optimization, marketing, standardization of natural and synthetic biologically active compounds". The themes are registered at the State Center for Scientific Research, Design, Applied and Dissertation Works under the Presidium of the National Academy of Sciences of the Republic of Azerbaijan (2006).

Publications. The main content of the dissertation was published as an article in a journal in the WoS database, as eight articles recommended by Supreme Attestation Commission of Azerbaijan, Russia and Belarus. In addition, the study materials were presented in six theses published in the collections, some of which are included in the largest international citation databases.

The name of the organization where the dissertation work was carried out. The dissertation work was conducted at the Department of Pharmacology and Toxicology of Research Centre of Azerbaijan Medical University**.**

The structure and volume of the dissertation work. The dissertation is presented in 165 pages of computer text and includes an introduction, literature review, study materials and methods, 3 chapters on the study itself, results, discussions of the study results, conclusions, practical recommendations, 180 bibliography, and the list of abbreviations. The work is documented in 27 tables, 5 formulas and illustrated with 6 figures.

The text of the dissertation consists of 180 762 characters, including: introduction – 12258, chapter I – 36091, chapter II – 12949, chapter III – 25254, chapter IV – 55896, chapter V – 21571, discussions of the results – 14178, conclusions – 2088, practical recommendations – 477 characters.

Materials and methods.

The experimental animals were split up into 4 series according to the Study's purposes and objectives. The studies were carried out on healthy, sexually mature white laboratory rats obtained from the Baku breeding facility and quarantined for 14 days in the vivarium of the Research Center of the Azerbaijan Medical University.

The 1st series, consisting of 130 rats and 130 mice, divided into 7 groups, was used to study the acute toxicity of mexidazole (LD_{50}) using the Spearman–Karber method. A control group of animals was created and divided into 2 subgroups (5 males and 5 females) that were housed in the exact same conditions as the main group in order to eliminate the distortions of the indicators caused by daily and seasonal rhythms. All animals in remaining groups also were divided into 2 subgroups with each consisting of 10 animals. There were only males in the 1st subgroup and only females in the 2nd subgoup. Mexidazole was given intraperitoneally in ascending doses at intervals of 50 mg/kg until all animals in the group died.

In the second series of studies, subchronic toxicity was assessed using the Lim R.K. method on 10 male rats. This method enables the evaluation of the cumulative effects of the tested substance.

In the third series of studies, the chronic toxicity of mexidazole was examined in comparison with cisplatine. Pathological changes in organs, tissues, and body systems were investigated under prolonged exposure to the toxicant, and the reversibility of these changes following its withdrawal was evaluated[6].

The studies were carried out on white outbred male laboratory rats:

1-1st group – intact group (10 rats).

The 2nd and 3rd main groups, each consisting of 50 rats, were administered mexidazole and cisplatine for 7, 15, and 30 days, respectively, at doses corresponding to 1/10 LD_{50}: 0.004/100 g body weight (for Mex) and 0.0007/100 g body weight (for Cis). After the treatment was discontinued, the animals' condition was monitored for 10 and 30 days.

At the end of the observation period, the animals were euthanized, and blood and organs were collected for laboratory and morphological studies. An express urine analysis was conducted at the specified intervals.

[6] Руководство по проведению доклинических исследований лекарственных средств / Под ред. А.Н.Миронова. – Ч.1, – Москва: Гриф и К, – 2012, – 944 с.

The integral indicators included data on changes in body weight, food and water intake, as well as an assessment of the general condition based on the animals' motor activity and respiratory rate.

Laboratory blood examinations were carried out on an Auto Hematology Analyzer Rayto RT -7600, (China, 2019). The following formed elements of the blood were determined:

WBC – white blood cell count
LYM – number of lymphocytes
MID – number of intermediate cells
GRA – number of granulocyte cells
LYM% – percentage share of lymphocytes
MID% – percentage share of intermediate cells
GRA% – percentage share of granulocyte cells
RBC – number of red blood cells (the number of erythrocytes)
HGB – hemoglobin content
HCT – hematocrit
MCV – mean corpuscular volume
MCH – mean corpuscular hemoglobin
MCHC – mean corpuscular hemoglobin concentration
RDW-SD – red cell distribution width, standard deviation
RDW-CV – red cell distribution width, coefficient of variation
PLT – number of platelets
MPV – mean platelet volume
PDW – platelet distribution width
PCT – Platelecrit
P-LCR – Platelet-Large Cell Ratio

Urine samples were gathered from animals housed in metabolic chambers equipped with built-in urine collectors.

Common urinalysis was conducted using True Line 10 M test strips (Turkey). These strips allow for the bilirubin, urobilinogen, protein, ketone bodies, nitrites, glucose, pH, urine density, and leukocyte count.

Daily urine creatinine levels were assessed using Erba Lachema standardized test kits (Czech Republic).

Creatinine levels in blood were determined using an enzymatic colorimetric method with Human chemical reagents, analyzed on StatFax chem.-well (Germany) analyzer.

To evaluate kidney function, creatinine and urea levels in both blood and urine were measured, and GFR was calculated.

A visual macroscopic examination of internal organs (liver, kidneys, heart, and others) was performed to assess changes in color, density, and shape. Organ sizes were measured using the classic technique – with a ruler on white paper.

The neurotoxicity of mexidazole was assessed using the "open field" method.

In the 4th series of experiments, the radioprotective properties of mexidazole were investigated in 260 white outbred rats.

The animals were divided into 5 groups: Group 1 (Intact): 10 animals (rats), serving as controls. Group 2 (Control): 10 rats, administered 1/30 LD_{50} of mexidazole. Groups 3, 4, and 5: Animals were subjected to a single irradiation dose of 2 Gy, 4 Gy, and 6.2 Gy, respectively. Animals in the groups from 3 to 5 also were further split into two subgroups of 40 animals each: The animals in the 1st subgroup opf each group were exposed to radiation while being in an intact state, and the animals in the 2nd subgroup were exposed to radiation against the background of intraperitoneal injection of 1/30 LD_{50} mexidazole a half-hour before the radiation.

Rats, with five animals per cage, were irradiated using an RUM-17 X-ray machine. At 8 hours, 1, 5, and 30 days post-irradiation, they were decapitated, and blood samples were collected for biochemical analyses.

Statistical analysis of the data utilized nonparametric methods: the Wilcoxon-Mann-Whitney criterion for comparing independent groups, and the sign test method alongside the Wilcoxon rank method for comparing dependent groups. These analyses were performed using MS EXCEL and S-PLUS software7.

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[7] Гублер, Е.В. Применение непараметрических критериев статистики в медико-биологических исследованиях / Е.В.Гублер, А.А.Генкин – Л.: Медицина, – 1973. – 144 с.

RESULTS AND DISCUSSION

Determination of acute toxicity

The LD_{50} of mexidazole was found to be 355 ±184.471 mg/kg for male mice and 385 ±189.957 mg/kg for female mice. For male rats, it was 405 ±188.457 mg/kg, and for female rats, 430 ±187.227 mg/kg. Based on the Hodge and Sterner toxicity scale, the compound is classified as moderately toxic.

Macroscopic examination of the internal organs (chest and abdominal cavities) of deceased animals revealed pathological changes inconsistent with life, with particularly significant damage observed in the liver and kidneys. It was established that the body weight of experimental animals decreased proportionally to the increased administered dose by the end of the observation period. No fur damage was observed in the surviving mice and rats across all the experimental groups.

Determination of subchronic toxicity

Cumulation coefficient - C_c

$$LD_{50}/LD_{50\,n} = 400/895 = 0.44, \text{ where}$$

$LD_{50\,-}$ single dose

$LD_{50\,n}$ - repeatedly administered dose

A C_C value less than 1 indicates that mexidazole accumulates in the body.

Determination of chronic toxicity

During the assessment of chronic toxicity, alterations were identified in blood cell composition, urine parameters, and behavioral responses.

The blood system is known to be labile and sensitive to toxic effects from exobiotics; specifically, cytostatic agents can depress hematopoiesis[8]. Therefore, a complete blood count was performed, including 17 indicators considered most informative for evaluating the compound's toxicity.

[8] Авдеева, О.И. Влияние цитостатиков на гэмопоэз аутобредных мышей / О.И.Авдеева, М.Н.Макарова, В.Г.Макаров // Фармация, – 2019, т.68. №2. с. 50-56.

The studies revealed that with mexidazole administration, there was a slight increase in WBC (10.54% with $p>0.05$), LYM (19.02% with $p<0.05$), and GRA (17.10% with $p>0.05$) levels on day 7. Subsequently, a significant decrease in these indicators was observed. By day 30 of administration, the levels differed from intact animals as follows: WBC by 45.8% ($p<0.001$), LYM by 27.8% ($p<0.005$), and GRA by 71.27% ($p<0.001$).

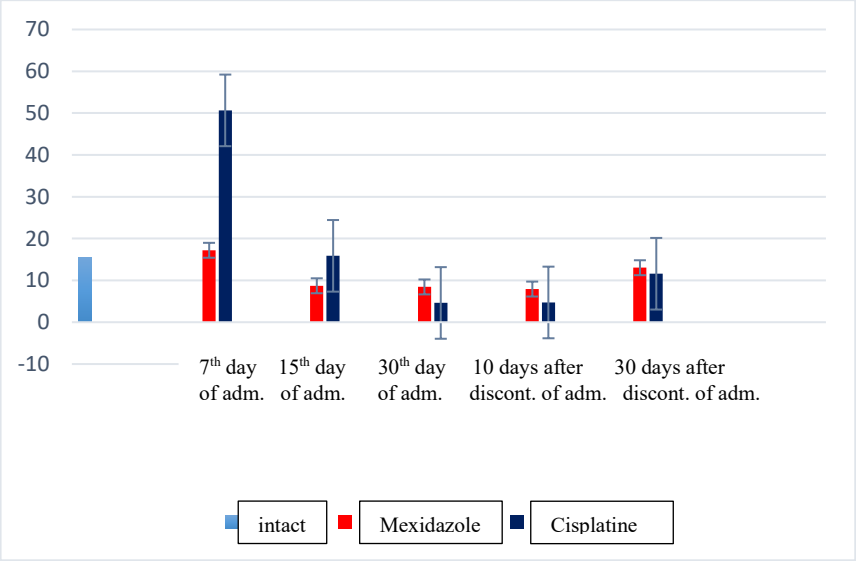

Diagram 1. The changes in white blood cell count (10^9/L) during the administration of Mexidazole and Cisplatine, including standard error

After discontinuing the administration of the complex compound, all studied parameters largely returned to initial values (IV) by the 30th day of observation, showing only minor differences. Specifically, WBC was 16.30% lower ($p>0.05$), LYM was 3.78% higher ($p>0.05$), and GRA was 4.44% higher ($p>0.05$).

When cisplatine was administered, similar trends toward pathological changes were observed, but the deviation from initial values was more pronounced. For instance, on the 7th day after cisplatine administration, WBC surged by 225.49% ($p<0.001$), LYM by 506.07% ($p<0.001$), and GRA by 129.34% ($p>0.05$). Subsequently, a sharp decline

in these counts occurred, with WBC decreasing by 70.39% ($p<0.001$), LYM by 83.53% ($p<0.001$), and GRA by 61.27% ($p<0.001$) by the 30th day of administration. A significant improvement in these indicators was noted by the 30th day following the discontinuation of cisplatine. At this point, WBC content was 25.23% less than initial values ($p<0.005$), LYM was 47.3% less ($p<0.001$), and GRA was 23.79% less ($p<0.05$).

The study also indicated that RBC (red blood cells) showed greater resistance to the negative effects of chemotherapy. The experimental data are summarized in Table 1 below.

Table 1.

The red blood cells count of the animals receiving Mexidazole

	Intact values	Mexidazole				
		Day 7	Day 15	Day 30	after 10 days	after 1 month
RBC (10^9/L)	7.20 (6.3-8.4)	7.79 (7.3-8.2) ***	8.10 (7.5-8.6) ***	7.39 (6.4-8.1)	7.30 (6.5-8.1)	7.08 (6.2-8.2)
HGB (g/L)	137.8 (129-153)	136.3 (128-144)	156.9 (148-169) ****	147.6 (133-159) **	145.1 (131-153) *	127.1 (122-135) ****
HCT (%)	39.38 (35.2-43.4)	39.70 (38.7-40.5)	44.22 (39.9-47.2) ****	42.37 (38.2-49.2) *	42.22 (37.3-47.5) *	38.61 (35.6-42.2)
MCV (fh)	56.26 (50.1-64.0)	50.32 (48.7-52.8) ****	53.09 (49.8-58.1)	57.15 (54.7-60.5)	58.01 (53.1-65.7)	52.30 (43.1-64.0)
MCH (pg)	19.25 (17.9-22.9)	18.24 (17.4-19.0)	18.83 (18.0-19.6)	22.88 (19.1-48.4) *	19.45 (17.3-22.0)	19.75 (18.0-22.0)
MCHC (g/L)	350.2 (331-375)	348.8 (339-355)	357.0 (343-366)*	349.6 (346-353)	348.7 (343-354)	343.1 (337-356)
RDW-SD(fl)	31.8 (28.0-36.9)	28.1 (26.4-30.9) **	29.3 (25.6-32.1)	34.4 (32.8-36.5)	33.4 (31.7-36.1)	28.9 (27.1-30.3) *
RDW-CV(%)	12.22 (11.0-13.0)	11.89 (10.9-12.6)	12.17 (11.6-12.7)	12.95 (12.4-13.2) ****	12.97 (12.7-13.2) ****	12.13 (11.0-13.5)

Note * – statistical significance of the difference as compared to intact animals. * –p<0,05; ** – p<0,01; *** – p<0,005; **** – p<0,001.

Table 1 demonstrates that during the first 15 days of mexidazole administration, RBC tended to increase significantly, by 12.5% ($p<0.005$), with values approaching intact levels by the 30th day. HGB

content (Table 1) showed minimal change compared to initial values, but a 7.76% decrease ($p<0.001$) was observed by the experiment's end.

HCT content (Table 1) remained largely unchanged on day 7, then significantly increased by 12.29% ($p<0.005$) on day 15, and by 7.59% ($p<0.05$) on day 30. After the discontinuation of mexidazole, on day 30, HCT was 1.96% lower than initial values ($p>0.05$).

In the group of animals administered cisplatine (Table 2), the RBC (red blood cell) content showed more pronounced changes. From day 7 to day 30 of cisplatine administration, RBC levels consistently declined, resulting in a 45.83% decrease by day 30 ($p<0.001$). However, after the drug was discontinued, RBC gradually and reliably recovered, ending the observation period 11.5% lower than initial values ($p<0.05$).

Table 2.

The red blood cells count of the animals receiving Cisplatine.

	Intact v.	Cisplatine				
		Day 7	Day 15	Day 30	after 10 days	after 1 month
RBC (10^9/L)	7.20 (6.3-8.4)	6.68 (5.9-7.4) *	5.23 (4.8-6.0) ****	3.90 (3.3-4.6) ****	5.38 (4.8-6.0) ****	6.37 (5.3-7.5) *
HCB. q/l	137.8 (129-153)	127.4 (111-148) ***	96.9 (87-113) ****	80.5 (54-100) ****	103.7 (88-115) ****	129.6 (110-171)
HCT. (%)	39.38 (35.2-43.4)	37.35 (32.8-42.4)	33.87 (26.7-38.1) ****	21.55 (20.1-24.1) ****	36.74 (31.1-41.9)	33.97 (30.1-40.3) ****
MCV. fh	56.26 (50.1-64.0)	48.82 (41.7-55.4) ***	38.48 (32.5-46.1) ****	23.22 (20.7-27.2) ****	44.09 (36.5-50.2) ****	45.77 (40.6-51.2) ****
MCH. pg	19.25 (17.9-22.9)	17.99 (15.3-20.3) *	14.15 (12.2-18.7) ****	9.22 (8.2-10.1) ****	15.41 (12.8-19.2) ****	16.17 (13.0-18.2) ****
MCHC. g/l	350.2 (331-375)	332.6 (314-351) **	248.3 (227-267) ****	180.6 (165-190) ****	250.2 (220-290) ****	323.1 (310-350) ****
RDW-SD. fl	31.8 (28.0-36.9)	29.2 (26.7-36.6) *	21.9 (18.7-26.7) ****	16.1 (13.2-20.1) ****	23.7 (20.1-27.3) ****	20.8 (17.1-28.1) ****
RDW-CV. %	12.22 (11.0-13.0)	10.83 (10.0-12.2) ***	8.45 (7.0-9.5) ****	6.36 (5.5-7.2) ****	9.76 (7.0-12.6) ***	10.96 (10.1-11.4) ****

*Note * – statistical significance of the difference as compared to intact animals. * –$p<0,05$; ** – $p<0,01$; *** – $p<0,005$; **** – $p<0,001$.*

The HCB content also clearly decreased throughout the entire period of cisplatine administration, dropping by 41.6% by day 30 ($p<0.001$). Following the discontinuation of cisplatine, HCB levels rose, and by the 30th day post-administration, they were 6% lower than initial values ($p>0.05$).

The hematocrit (HCT) level mirrored the changes observed in HCB, ending the experiment with a 13.74% reduction compared to initial values ($p<0.001$).

When examining platelet (PLT) count in rats given mexidazole (diagram 2), an insignificant decrease was noted on study days 7 and 15, specifically by 8.35% and 12.24% respectively ($p>0.05$). Subsequently, blood PLT levels rose, surpassing initial values by 1.82% on day 30 of administration ($p>0.05$). Notably, after the drug was stopped, platelet counts declined by 11.18% on day 10 of observation ($p>0.05$) and by 16.93% on day 30 ($p<0.001$).

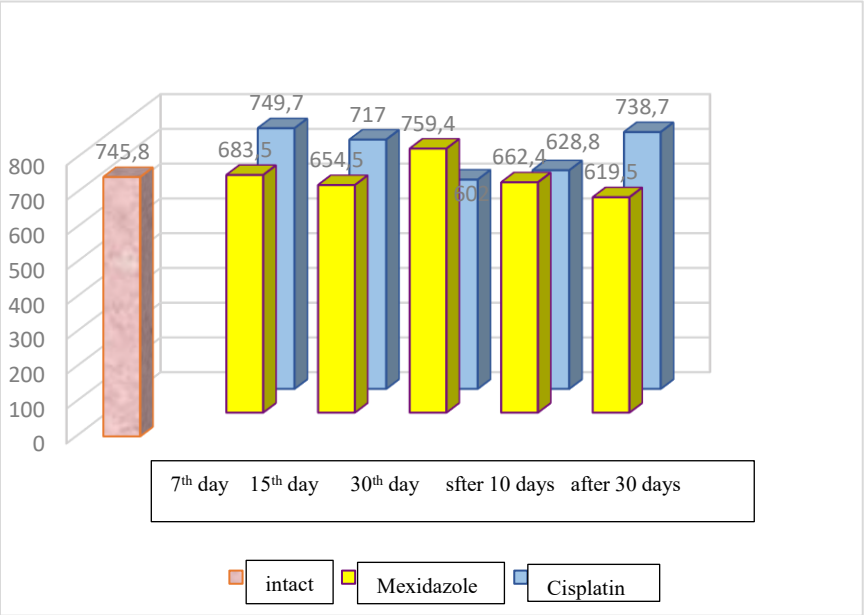

Diagram 2. Platelet count of the animals receiving Mexidazole and Cisplatine

Under the influence of cisplatine (diagram 2), the PLT (platelet) count initially saw a slight increase on day 7 of administration. This was followed by decreases of 3.86% on day 15 and 19.28% on day 30. 10 days after the discontinuation of the drug, PLT count decreased by 15.7%. A month after the discontinuation of cisplatine, platelet levels began to recover but did not reach the initial levels. All observed changes in PLT with cisplatine lacked statistical significance.

Comparing the results from group 2 (receiving Mex) and group 3 (receiving Cis), it's evident that group 2 experienced less severe disturbances in blood cell composition and indices. Moreover, there is a discernible association between a few indicators: WBC (10^9/L) – LYM (10^9/L): $\rho=0.83$; $p<0.01$ (significant positive correlation); LYM (10^9/L) – MID (10^9/L): $\rho=0.578$; $p<0.05$ (significant positive correlation); MCV (fh) – MCH (pg): $\rho=0.661$; $p<0.05$ (significant positive correlation); RDW-SD(fl) – RDW-CV(%): $\rho=0.309$; $p>0.05$; PDW (%) – PCT (%): $\rho=-0.442$; $p>0.05$, indicating that these parameters are important for tracking the level of intoxication under the exposure to studied compounds.

Urine and blood examinations.

Urine parameters are crucial for evaluating a substance's toxic effects on the body[9]. Key parameters include changes in color, pH level, urine volume, and the presence of sediment.

Compared to the intact group, both study groups showed a similar reduction in the volume of daily urine.

A pathological shift in urine color from the normal straw-yellow was observed in both groups. However, when mexidazole was used, this change was significantly less pronounced and appeared later.

Normally, urine is slightly acidic[10]. Throughout the entire experiment, urine pH remained within this physiological norm for both groups.

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[9] Бурнашева, Е.В. Поражение почек при противоопухолевой терапии / Е.В. Бурнашева, Ю.В.Шатохин, И.В.Снежко, А.А.Мацуга // Нефрология, – 2018. т.22, №5, – с. 17-24.

[10] СПРАВОЧНИК. Физиологические, биохимические и биометрические показатели нормы экспериментальных животных / Т.В.Абрашова, Я.А.Гущин, М.А.Ковалева [и др.]. – СПБ.: Изд-во «ЛЕМА», – 2013. – с 116.

As depicted in Diagram 3, the highest amount of sediment in both groups was observed on day 30 of administration. Specifically, the mexidazole group had "a lot" of sediment in 40% of animals, while the cisplatine group showed this in 70% of animals. The amount of sediment decreased during the observation period.

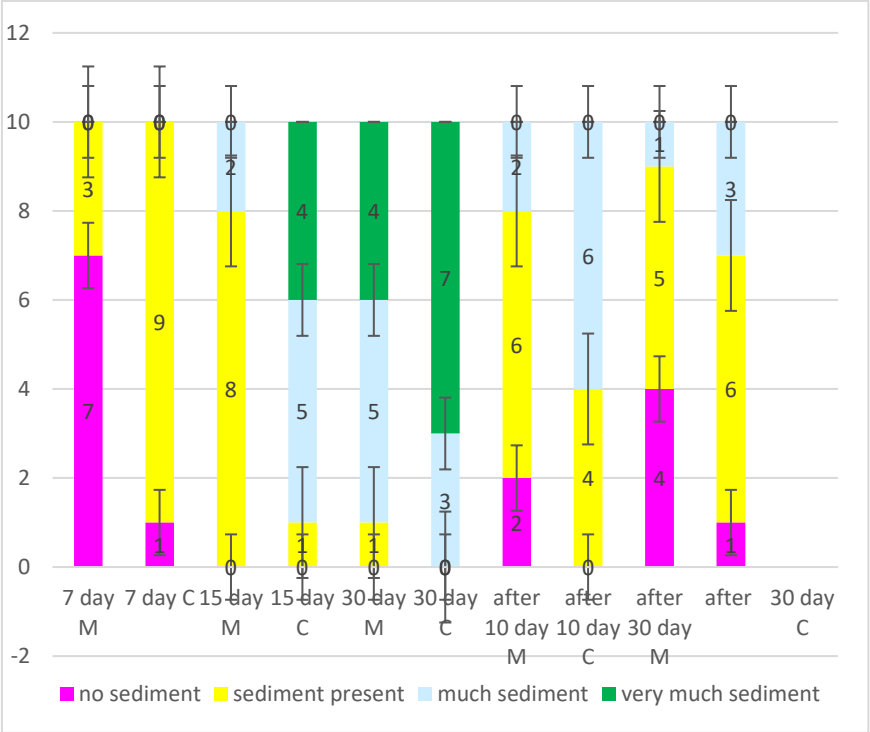

Diagram 3. The content of sediment in 24h-urine of animals against the background of Mexidazole and Cisplatine administration

Leukocyte content dynamically increased in both groups. With cisplatine administration, leukocytes appeared earlier and in greater quantities. Thus, On the 7th day, leucocytes in the urine were detected in 30% of the animals in the second group. In the following days of Mexidazole administration, a significant increase in leukocytes was observed ($p=0.043$), and one month after stopping the administration,

they were not detected in any of the animals (p>0,05). In the third group, receiving cisplatine, leukocytes in the urine were detected in 50% of the animals on the 7th day. Subsequently, during the days of administration, their number continued to increase. At the end of the experiment, leukocytes were present in the urine of 60% of animals (40% had a small amount, p=0.043; 20% had a large amount, p>0.05)

With the administration of mexidazole urobilinogen, bilirubin, protein, and blood were detected significantly less often in urine samples in comparison with cisplatine. This finding, presented in Table 3, suggests that the new complex compound, mexidazole, has a lower damaging impact on the liver and kidneys. Thus, one month after discontinuation of mexidazole administration, no blood was detected in the urine of any animal, whereas cisplatine treatment it was observed in 50% of the animals. At this time point, a significant amount of bilirubin was detected in only 20% of animals in group 2 (p>0.05), whereas in group 3 it was obserwed in 80% of animals. At the end of experiment. Protein was detected in both groups in group 2 in half of the animals, and in group 3 – in 100% of the animals.

Determination of creatinine concentration in blood, along with calculating the glomerular filtration rate, allows for an objective assessment of kidney function and the extent of any damage.

As shown in Table 3, on day 7 of mexidazole administration, animals displayed a 40% increase in blood creatinine compared to the intact group (p>0.05), while urine creatinine remained unchanged. Concurrently, GFR decreased by 40% (p<0.001). By day 15, blood creatinine concentration had risen by 87% over the control (p<0.001), urine creatinine increased by 6.3%, and GFR saw a 60% reduction (p<0.001). Blood creatinine continued to rise by day 30, exceeding initial levels by 173% (p<0.001), urine creatinine increased by 40%, and GFR dropped by 70% (p<0.001). 10 days after mexidazole was discontnued, blood creatinine remained 187% higher (p<0.001), while urine creatinine began to decline but was still 20% above initial levels (p<0.05). GFR stayed reduced by 60% (p<0.001). A month later, indicators improved: blood creatinine was 13% lower than initial levels (p>0.05), urine creatinine nearly normalized, while GFR remained 30% lower (p>0.05).

Table 3.

Results of the determination of creatinine levels in urine and blood, and calculations of glomerular filtration rate (GFR) in animals against the background of Mexidazole and Cisplatin administration

	Creatinine				GFR Mex mL/min	GFR Cis mL/min
	Mex		Cisplatine			
	Blood mmol/L	Urine mmol/L	Blood mmol/L	Urine mmol/L		
Intact v.	0.15 (0.10-0.25)	1.6 (1.0-2.0)	0.15 (0.10-0.25)	1.6 (1.0-2.0)	0.10 (0.07-0.15)	0.10 (0.07-0.15)
Day 7	0.21 (0.1-0.25)	1.5 (1.0-2.0)	0.48 ** (0.25-1.00)	1.6 (1.0-2.0)	0.06 ** (0.02-0.13)	0.03 ** (0.01-0.6)
Day 15	0.28 ** (0.2-0.45)	1.70 (1.0-2.0)	0.64 ** (0.36-0.1)	1.90 * (1.0-3.0)	0.05 ** (0.02-0.07)	0.02 ** (0.01-0.05)
Day 30	0.41 ** (0.28-0.80)	2.10 * (1.0-3.0)	0.85 ** (0.49-1.10)	2.60 ** (2.0-3.0)	0.03 ** (0.02-0.06)	0.02 ** (0.01-0.04)
10 days after discontinuation	0.43 ** (0.25-0.69)	1.80 * (1.0-2.0)	0.72 ** (0.47-1.00)	2.60 ** (2.0-3.0)	0.04 ** (0.02-0.06)	0.03 ** (0.01-0.05)
1 month after discontinuation	0.13 (0.10-0.19)	1.50 (1.0-2.0)	0.52 ** (0.27-0.85)	2.10 * (1.0-3.0)	0.07 (0.04-0.10)	0.04 ** (0.02-0.06)

Note.

P *– statistical significance as related to intact values*

** - p<0,05, ** - p<0,001*

In animals treated with cisplatine (Table 3) a significant 220% increase in blood creatinine ($p<0.001$) and a slight 6.6% increase in urine creatinine were noted as early as day 7. GFR decreased by 70% ($p<0.001$). By day 15, blood creatinine exceeded intact values by 326% ($p<0.001$), urine creatinine by 27% ($p<0.05$), and GFR declined by 80% ($p<0.001$). By day 30, blood creatinine concentration reached 466% of control levels ($p<0.001$), urine creatinine rose by 73% ($p<0.001$), and GFR was still reduced by 80% ($p<0.001$). 10 days after cisplatine was discontinued, blood creatinine decreased but was still 380% above normal ($p<0.001$), urine creatinine remained 73% higher, and GFR stayed reduced by 70% ($p<0.001$). One month later, parameters partially normalized: blood creatinine was 246% above intact levels ($p<0.001$), urine creatinine was 31% higher ($p<0.05$), and GFR was still reduced by 60% ($p<0.001$), indicating incomplete kidney function recovery.

In conclusion, the administration of mexidazole resulted in less pronounced and partially reversible changes in kidney function compared to cisplatine, which is supported by the observed creatinine levels and GFR reductions.

Determination of neurotoxicity

We assessed the neurotoxicity of the tested substances by observing behavioral reaction changes in rats using the "open field" test, with observations recorded three times at 30-minute intervals. This test evaluates several indicators: the number of squares crossed, hole exploration, vertical activity, grooming, and the number of fecal boli.

When assessing the effect of mexidazole on the behavioral motivation of rats in the open field test, a significant reduction in all parameters of locomotor activity of the rodents was observed by day 7 of the experiment. Specifically, there was a clear decrease in both horizontal and vertical activity, along with reduced exploratory behavior (hole sniffing) and grooming. Concurrently, the number of fecal boli-an indicator of anxiety-doubled ($p < 0.001$). This pattern persisted throughout the observation period, including on days 15 and 30, as well as 10 days after drug withdrawal. The overall neurotropic effect of mexidazole on spontaneous activity gradually normalized,

with the exception of grooming behavior, which remained significantly reduced (nearly threefold decrease, $p < 0.001$). Full recovery was observed only by day 30 after treatment cessation ($p < 0.05$; see Diagram 4).

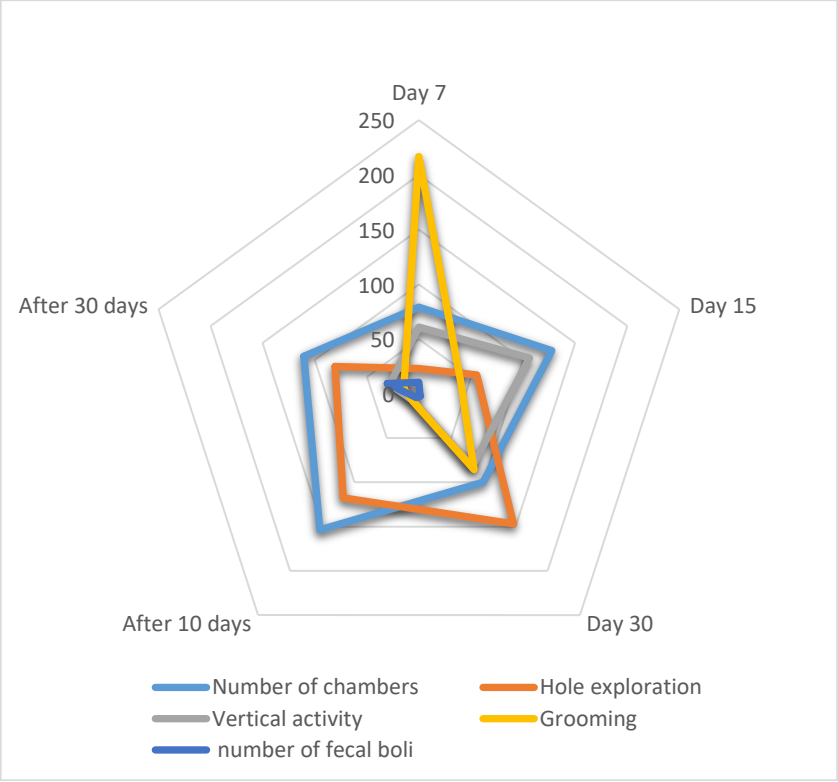

Diagram 4. Changes in the behavioral reactions of the animals against the background of Mexidazole and Cisplatine administration observed during the open field tests

A more significant negative impact was observed when cisplatine was studied for its effect on rats' spontaneous behavior. For example, by day 7, both horizontal and vertical movements decreased by over twofold ($p<0.001$), hole exploration dropped by 35% ($p<0.001$), and grooming was almost entirely absent (a 91% decrease) ($p<0.001$). The number of fecal boli also doubled ($p<0.001$).

This suppression of behavioral motivation of the rats continued through the 15th and 30th days of cisplatine administration, showing a severe reduction in motor activity (more than threefold, $p<0.001$), decreased hole exploration, and significantly reduced grooming ($p<0.001$). Consistent with earlier observations, the number of fecal boli remained elevated ($p<0.001$).

It is particularly important to note that, unlike the effects of mexidazole, the suppression of behavioral motivation caused by cisplatine was not restored even after stopping its administration on the 10th and 30th days of observation.

Therefore, we can conclude that mexidazole did not suppress the spontaneous behavioral activity of experimental rats after its administration was stopped, a clear difference from cisplatine.

Taking into account that in the open field tests of toxicity, the reductions in the numbers of squares crossed, lower exploratory behavior, and vertical activity are indicative of decreased dynamic activity, and the increases in the number of boluses and reduction of the grooming frequencies reflect increased anxiety, it might be concluded that both compounds exert an inhibitory action on the CNS, while such action is more pronounced after cisplatine administration, with more evident effects on the centres of motion and exploratory activity. The diagram also demonstrates that the changes inflicted by cisplatine are more persistent than those caused by the use of Mexidazole.

Determination of radioprotective activity.

Radioprotective activity refers to a substance's pharmacological action aimed at protecting body tissues from exposure to ionizing rays, such as radiation.

Modern radiodiagnostic methods like computed tomography, X-ray, and radiation therapy can lead to excessive body irradiation. When exposed to radiation, the hematopoietic system, including the red bone marrow, is among the first to be affected, leading to changes in the blood picture.

Currently, various compounds with anti-radiation effects, known as radioprotectors (medical means of anti-radiation protection),

are used to prevent radiation damage[11]. These substances can operate through different mechanisms, such as reducing oxidative stress or stimulating tissue regeneration, and so on., all of their pharmacological effects aimed at protecting the body from the harmful effects of radiation. The chemical structure of Mexidazole suggests it might possess a radioprotective effect, which requires experimental evidence.

In preparation for the experiment, before evaluating the effect of X-ray irradiation on blood cell content, we first determined how these indicators would change solely with the administration of Mexidazole at a dose of 1/30 LD_{50} (Table 4).

Table 4.

Changes in the haematic picture after intraperitoneal administration of Mexidazole at a dose of 1/30 LD_{50}

	Intact v.	Against the background of Mex administration			
		After 8 hours	After 24 hours	After 5 days	After 1 month
WBC 10^9/L	15.95 (12.0-22.6)	16.29 (12.0-22.7)	16.71 (12.0-20.9)	16.19 (12.2-21.8)	16.11 (10.7-22.1)
%		2.12	4.76	1.50	1.00
P		0.880	0.344	0.631	0.705
LYM 10^9/L	8.49 (6.3-11.3)	8.47 (6.4-11.2)	8.71 (6.4-11.4)	8.47 (5.9-12.0)	8.32 (6.0-12.3)
%		0.21	2.62	0.21	1.98
P		0.880	0.820	0.850	0.820
RBC 10^9/L	7.05 (6.4-8.3)	6.97 (6.0-8.5)	6.68 (5.9-8.0)	6.51 (5.7-7.8)	6.96 (6.3-7.9)
%		1.13	5.25	7.66	1.28
P		1.000	0.209	0.069	0.879
PLT 10^9/L	833.8 (710-988)	838.0 (730-1000)	834.0 (740-980)	840.0 (740-980)	844.0 (710-1010)
%		0.50	0.02	0.74	1.22
P		0.909	0.910	1.000	1.000

P *– statistical significance.*

% - the differences between the groups in percentages.

[11] Владимиров, В.Г., Красильников, И.И. О некоторых итогах и перспективах развития профилактической радиационной фармакологии // Обзор по клинической фармакологии и лекарственной терапии, – 2011, т.9, № 1, – с. 44-50.

The observations of the animals demonstrated that all 100 rats in this group survived up to the end of the experiment. The visual observations also did not reveal any changes in the wight, fur condition, food and water intake, number of boli, and behavioral reactions. The results of biochemical blood test also failed to reveal any substantial deviations in initial values.

The results of biochemical blood tests demonstrated that the changes taking place in both groups (1st subgroup – the animals that did not receive Mex, 2nd subgroup – the animals that received Mex) against the background of the radiation exposure at a dose of 2 Gy do not deviate from the initial values substantially, and are not life-threatening for the animals.

Upon exposure to X-rays at a dose of 2 Gy, the WBC count in the blood of animals in the first subgroup hardly changed after 8 hours ($p>0,05$). On the 5th day, the WBC count continued to rise, exceeding the intact values by 7% ($p >0,05$). This indicator in the blood analysis decreased by 6,39% from the intact values after one month ($p >0,05$).

In the second subgroup, where animals received mexidazol before irradiation, the WBC count in the blood slightly decreased compared to the intact values: by 10,7% after 8 hours ($p >0,05$), by 12,2% after 24 hours ($p >0,05$), and by 12,9% after 5 days ($p >0,05$). By the end of the month, this indicator began to increase and was 6,65% lower than the intact values ($p >0,05$).

The percentage difference between the values of the second subgroup and the statistical significance of this difference indicate that, under X-ray irradiation at a dose of 2 Gy with mexidazol administration throughout the experiment, the WBC count in the blood differs both in the dynamics of changes and in quantitative values compared to animals that did not receive mexidazol. By the end of the 30th day, these changes tended to return to the intact values.

The LYM count in the blood of animals in the 1st subgroup decreased compared to baseline after irradiation: by 37.8% at 8 hours ($p<0.001$), by 48.5% at 24 hours ($p<0.001$), and by 51.4% on day 5 ($p<0.001$). After one month, partial recovery was observed, but levels remained 18,6% below baseline ($p<0.05$). In contrast, in the 2nd subgroup, LYM levels increased by 10% at 8 hours ($p>0.05$), by 8,8%

at 24 hours (p>0.05), by 9,1% on day 5 (p>0.05), and by 10% at 30 days (p>0.05). Comparison of the results of the first and second subgroups revealed that the differences between them at certain time points were significant and statistically reliable.

Data analysis showed that the differences in the blood levels of leukocytes and lymphocytes were insignificant and not statistically significant.

Red blood cell and platelet counts in both the first and second subgroups remained within the normal range across all studied time periods, with minor fluctuations lacking any statistical significance.

Irradiating the animals with 4 Gy X-rays resulted in more significant changes (Table 5).

Table 5.

Changes in the haematic picture after the radiation exposure at a dose of 4 Gy

		WBC 10^9/L	**% P**	**LYM 10^9/L**	**% P**	**RBC 10^9/L**	**% P**	**PLT 10^9/L**	**% P**
After 8 hours	Without Mex	23.78 (19.4-27.1)	28.4	2.86 (1.8-4.3)	158	8.38 (7.2-9.0)	17.4	1061.0 (960-1200)	22.4
	With Mex	17.02 (15.3-18.9)	0.0002	7.38 (6.1-8.7)	0.0002	6.92 (6.4-7.3)	0.0004	823.0 (740-960)	0.0002
After 24 hours	Without Mex	35.57 (29.7-40.5)	55.4	2.34 (1.9-2.9)	189.7	9.16 (7.5-10.5)	24.1	1007.0 (900-1200)	13.6
	With Mex	15.88 (12.9-18.7)	0.0002	6.78 (5.8-8.5)	0.0002	6.95 (6.3-7.5)	0.0002	870.0 (750-920)	0.0004
After 5 days	Without Mex	15.82 (13.7-17.7)	0.8	1.92 (1.7-2.1)	236.5	8.00 (6.5-8.9)	19.4	853.0 (730-970)	8.8
	With Mex	15.95 (13.1-17.9)	0.7052	6.46 (5.2-7.9)	0.0002	6.45 (1.9-8.0)	0.0035	778.0 (700-870)	0.0579
After 1 month	Without Mex	6.13 (2.3-8.3)	168	5.55 (3.9-7.2)	46.1	6.86 (4.5-8.3)	1.6	730.0 (650-810)	8.6
	With Mex	16.48 (14.4-18.0)	0.0002	8.11 (6.4-10.5)	0.0005	6.97 (6.4-7.5)	0.9395	793.0 (710-930)	0.0875

In the 1st subgroup, WBC increased by 49.1% compared to the IV after 8 hours (p<0.001), and by 123% after 24 hours (p<0.001). Subsequently, a decrease in WBC was noted, with its levels approaching the IV by day 5 (p>0.05). After one month, a 61.6% decrease was observed (p<0.001). Conversely, in the second subgroup, WBC increased by 6.7% after 8 hours (p>0.05). After 1 and

5 days, it decreased to nearly 33% ($p>0.05$), and after one month, it increased by 3.3% ($p>0.05$).

The difference between the leukocyte values of these subgroups is presented in Table 5.

The dynamics of LYM changes mirrored those of WBC.

The difference between the lymphocyte values of these subgroups is presented in Table 5.

In the first subgroup, the levels of RBC initially increased after 8 and 24 hours, then decreased, ending 2.7% lower than the intact group (IV) by day 30 ($p>0.05$). Conversely, in the 2nd subgroup, RBCs changed little compared to the IV. Even these small changes in RBC in the groups, when compared, indicate mexidazole's radioprotective effect.

Specifically, the RBC content in the blood of animals receiving mexidazole was lower than in animals that did not receive it: after 8 hours: 17.4% lower ($p=0.0004$); after 24 hours: 24.1% lower ($p=0.0002$); after 5 days: 19.4% lower ($p=0.0035$); after one month: 1.6% lower ($p=0.9395$).

Changes in platelets (PLT) were insignificant in both the 1st and 2nd subgroups (Table 5)

The data confirm that the preliminary use of mexidazole significantly reduces the negative impact against the background of 4 Gy irradiation on the values of all studied blood parameters.

Against the background of 6.2 Gy X-ray irradiation (Table 6), WBC changes were less active in the 2nd subgroup.

However, in the 1st subgroup, significant changes occurred: after 8 hours: WBC count increased by 111.6% compared to the IV ($p<0.001$); after 24 hours: Increased by 415.5% ($p<0.001$); on day 5: Increased by 474.7% ($p<0.001$). After one month: a sharp decrease of 71% from the IV was noted ($p<0.001$).

In contrast, within the second subgroup the WBC count increased by 27.7% after 8 hours ($p<0.001$), then remained almost unchanged after 1 day. By day 5, it decreased by 24.8% from the intact group (IV) ($p<0.001$), and after a month, it approached the IV, being 4.3% lower ($p>0.05$).

The difference between the leukocyte values of these subgroups is presented in Table 6.

The lymphocyte count underwent changes after of irradiation. In the first subgroup, 8 hours after irradiation, the lymphocyte count decreased by 86.5% ($p<0.001$). After 24 hours, this indicator continued to decline, being 92.3% lower than intact values ($p<0.001$), and on the 5th day it remained almost unchanged. Blood test results after one month showed that the lymphocyte count had increased, but still remained 66.3% below the intact values ($p<0.001$).

Table 6.

Changes in the haematic picture after the radiation exposure at a dose of 6,2 Gy

		WBC 10^9/L	% P	LYM 10^9/L	% P	RBC 10^9/L	% P	PLT 10^9/L	% P
after 8 hours	Without Mex	33.75 (29.7-36.7)	39.6	1.15 (0.5-1.9)	371.3	8.61 (7.1-10.1)	17.9	1160 (1000-1300)	22.1
	With Mex	20.37 (18.7-25.0)	0.0002	5.42 (4.8-6.3)	0.0002	7.07 (6.4-8.5)	0.0016	904 (750-1000)	0.0003
after 24 hours	Without Mex	82.23 (70.7-90.9)	75.4	0.65 (0.2-1.0)	689.2	3.23 (2.3-4.5)	115.5	1182 (1000-1300)	23.4
	With Mex	20.22 (16.5-23.4)	0.0002	5.13 (4.6-6.1)	0.0002	6.96 (6.5-7.7)	0.0002	905 (810-1000)	0.0003
after 5 days	Without Mex	91.67 (83.7-101.3)	86.9	0.66 (0.3-0.9)	672.7	3.11 (2.0-4.3)	123.2	944 (890-1000)	12.5
	With Mex	11.99 (10.1-14.5)	0.0002	5.10 (4.7-6.0)	0.0002	6.94 (6.3-7.9)	0.0002	826 (730-970)	0.0016
after 1 month	Without Mex	4.63 (3.7-5.4)	229.8	2.86 (1.7-3.9)	116.4	5.34 (4.8-6.2)	31.1	286 (120-410)	149
	With Mex	15.27 (12.7-18.1)	0.0002	6.19 (5.0-7.0)	0.0002	7.00 (6.6-7.3)	0.0002	712 (620-810)	0.0002

In the second subgroup, where the animals received mexidazol before irradiation, the lymphocyte count in the blood changed as follows: after 8 hours it decreased 36.2%, after 1 day being 39.6% lower than the intact values ($p<0.001$), and on the 5th day remained almost unchanged. Blood test results after one month showed that the lymphocyte count had decreased by 27.1% ($p<0.001$).

The difference between the LYM values of these subgroups is presented in Table 6.

The erythrocyte count in the blood of animals under irradiation changed as follows (Table 6). In the first subgroup, 8 hours after irradiation, the erythrocyte count increased by 22.1% ($p<0.001$). After 24 hours, this indicator decreased by 54.2% compared to the intact values ($p<0.001$); on day 5th, it decreased by 55.9% ($p<0.001$). Blood test results after one month showed that the erythrocyte count had increased but was still 24.3% lower than the intact values.

In the second subgroup, where the animals received mexidazole before irradiation, the erythrocyte count in the blood changed little.

The difference between the RBC values of these subgroups is presented in Table 6.

The platelet count in the blood of animals under irradiation changed as follows. In the first subgroup, 8 hours after irradiation, the platelet count increased by 39.12% ($p<0.001$). After 24 hours, this indicator exceeded the intact values by 41.7% ($p<0.001$); on the 5th day, the platelet count decreased, remaining 13.2% above the intact values ($p>0.05$). Blood test results after one month showed that the platelet count had decreased by 66% compared to the intact values ($p<0.001$)

In the second subgroup, where the animals received mexidazole before irradiation, the platelet count in the blood changed little. After one month, it was 14.6% lower than the intact values ($p<0.05$).

The difference between the PLT values of these subgroups is presented in Table 6.

Ultimately, mexidazole provides a significant protective effect on the composition of blood cells when exposed to radiation. Furthermore. this protective activity becomes more pronounced with increasing radiation intensity.

CONCLUSIONS

1. Mexidazole's acute toxicity is statistically significantly lower than cisplatin's. For male mice, the LD_{50} is 355 ±184.471 mg/kg, and for females, it's 385 ±189.957 mg/kg. For male rats, the LD50 is 405 ±188.457 mg/kg, and for female rats, 430 ±187.227 mg/kg.

- A dose equivalent to 1/10 of the LD_{50} is considered a tolerable dose for mexidazole.
- Necrotic damage to the liver and kidneys was identified as the cause of death in animals suffering from mexidazole intoxication [1,2,12].

2. Studies of subchronic toxicity revealed that mexidazole accumulates in the bodies of animals, with an accumulation coefficient C_c of less than 1 [1]
3. Experiments on chronic toxicity established that mexidazole exhibits significantly less
4. nephrotoxicity, hepatotoxicity, and neurotoxicity as compared to cisplatine.
   - Animals treated with mexidazole displayed less pronounced disruptions in the composition and indices of formed elements of their blood [4, 6, 7].
   - The levels of leukocytes, urobilinogen, bilirubin, protein, and blood in the urine were statistically significantly lower with Mexidazole administration [8, 13].
   - By the end of observations, GFR in animals receiving cisplatine was 60% less than the intact group, whereas in Mexidazole-treated animals, GFR was 30% less [11]. This confirms that Mexidazole causes less damage to the liver and kidneys, indicating its lower toxicity.
   - Mexidazole possesses a certain degree of neurotropicity, expressed by the inhibitory effect on the centres of motion and exploratory activity against the background of increased anxiety. However, these changes are less pronounced, and are leveled off in a shorter time in comparison with cisplatine administration [9].
5. Mexidazole possesses a strong radioprotective effect. When mexidazole was administered at a dose of 1/30 LD_{50} before irradiation, it significantly reduced the pathological changes in the quantitative composition of blood cells caused by radiation exposure. For instance, after a single exposure to 4 Gy and 6.2 Gy X-rays, the differences in blood parameters on day 30 between the animals that received mexidazole and those that didn't were as

follows: Leukocytes: 168% (p=0.0002) and 229.8% (p=0.0002), lymphocytes: 46.1% (p=0.0005) and 116.4% (p=0.0002), erythrocytes (RBC): 1.6% (p=0.9395) and 31.1% (p=0.0002), platelets (PLT): 8.6% (p=0.0875) and 149% (p=0.0002). A direct correlation was observed, indicating that the protective effect of mexidazole increases with higher radiation intensity [10].

PRACTICAL RECOMMENDATIONS

1. Given mexidazole's relatively low toxicity, it should be further investigated for its potential use as an antitumor agent in clinical practice. Its antitumor activity has already been demonstrated through a mathematical model developed under Dr. Tuzun's guidance (Tuzun et al., 2023).
2. When prescribing cytostatic drugs, it's essential to regularly perform a complete blood count to monitor formed elements. This helps in assessing the body's intoxication level.

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The dissertation is available for review at the library of Azerbaijan Medical University

The electronic version of the dissertation and the abstract have been posted on the official website of the Azerbaijan Medical University (amu.edu.az).

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LIST OF ABBREVIATIONS

CIS	- cisplatin
GFR	- glomerular filtration rate
Gy	- Gray
HCT	- hematocrit
HGB	- hemoglobin content
IV	- intact values
LD_{50}	- median lethal dose
LYM	- number of lymphocytes
Mex	- Mexidazole
PLT	- number of platalets
RBC	- number of red blood cells (number of erythrocytes)
WBC	- number of white blood cells (number of leukocytes)

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