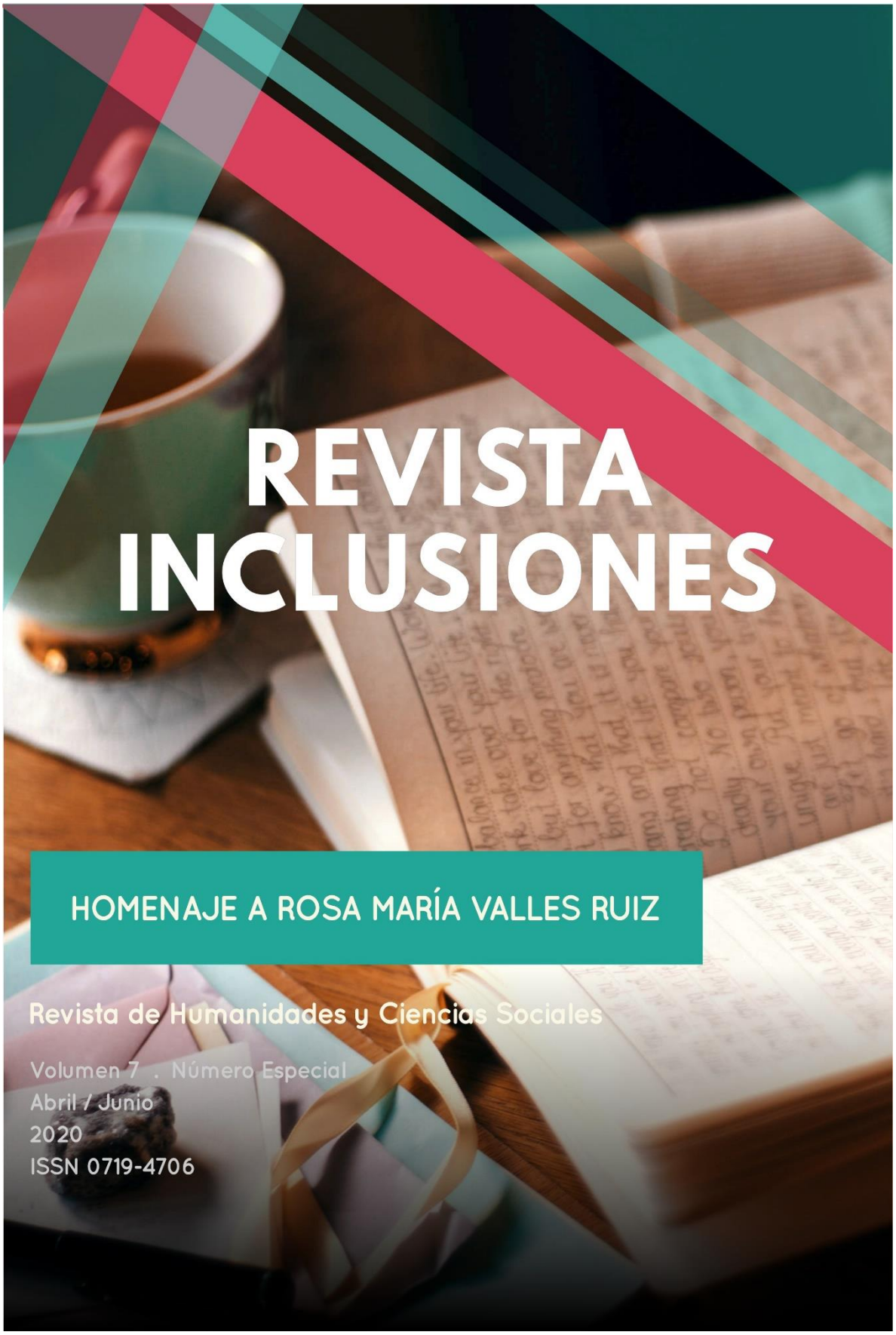

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COMPARATIVE ANALYSIS OF THE CHRONIC TOXICITY OF THE INGAVIRIN, RIMANTADINE, TRIAZAVIRIN, AND MOXIFLOXACIN DRUGS

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Abstract

The authors have aimed at comparing the new Triazavirin antiviral drug with already proven ones, such as Ingavirin and Rimantadine. Moxifloxacin, 4th generation fluoroquinolone, was used as antibacterial drugs. Outbred white mice were used as laboratory animals. During the experiment, one control and four experimental groups were formed based on analogues, five females and five males in each. The drugs were administered to the mice intragastrically, using a probe, previously diluted in 0.2 ml of saline. The drugs were administered to the experimental mice once a day, for 21 days. Slaughter by decapitation took place on day 22, and blood was drawn for laboratory tests. During the trial use of Ingavirin, Rimantadine, Triazavirin, and Moxifloxacin in recommended doses in laboratory animals (outbred mice), the Triazavirin drug has positively proved itself. Triazavirin is safe and does not cause changes in white and red blood cells. When using Triazavirin, biochemical blood parameters are within the species physiological range. The ALT and ALP level decreases, and cholesterol corresponds to the control.

Keywords

Laboratory mice – Antiviral drugs – Ingavirin – Rimantadine – Triazavirin – Moxifloxacin

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Introduction

The current developments in medicine and veterinary science have provided significantly wide arsenal of antimicrobial drugs to treat various diseases of animals and humans[1] . However, it should be noted that viral infections are becoming leaders among infectious diseases, and animal viruses actively mutate and lead to the emergence of new diseases in humans. In veterinary science, the issue of selecting and searching for effective, safe, and economically acceptable medicinal antiviral drugs is relevant. Vaccination is actively used in veterinary practice, but the load on the animal organism as per the planned treatment is enormous.[2] In the prevention and treatment of viral diseases in farm animals, interferons are actively used, and the list of drugs directly aimed at viruses is very restricted. Many drugs have proven themselves in the treatment of viral infections in humans, and the use thereof in veterinary practice would be a productive approach. Combinations of antiviral and antimicrobial drugs are very popular in medicine and veterinary science, such as, for example, Ribaflox, containing Ribavirin, as antiviral component and Enrofloxacin, being the 3rd generation fluoroquinolone acting on gram-positive and gram-negative microflora, as antibacterial one[3].

Based on the existing experience, the authors aimed at comparing the new Triazavirin antiviral drug with already proven ones, such as Ingavirin and Rimantadine. Of the antibacterial drugs, the authors fixed upon Moxifloxacin, the 4th generation fluoroquinolone, which was actively used to treat humans and animals.

It is necessary to comprehensively and comparatively evaluate their impact on some physiological indicators. To achieve this goal, the following tasks were set: to compare hematological, biochemical, hormonal blood counts when using these drugs in laboratory animals (white mice), and to assess the indicators and risks of pathophysiological abnormalities when using the drugs in healthy experimental animals[4].

[1] N. V. Danilevskaya y V. V. Subbotin, “Antibakterialnaya terapiya v veterinarnoy praktike”, Effektivnaya farmakoterapiya v veterinarii num 1 (2011): 38-43.

[2] T. I. Glotova; V. N. Silnikov; L. S. Koroleva; O. V. Kungurtseva; V. L. Tikhonov y A. G. Glotov, “Protivovirusnaya aktivnost novogo khimicheskogo soyedineniya”, Rossiyskiy veterinarnyy zhurnal num 1 (2012): 22-24; Otsenka toksichnosti i opasnosti khimicheskikh sredstv i ikh smesey dlya zdorovya cheloveka. Rukovodstvo (Moscow: Federal Center for Hygiene and Epidemiology of Rospotrebnadzor, 2014); T. I. Reshetnikova, “Gematologicheskiye, immunologicheskiye i gormonalnyye pokazateli krovi telyat pri primenenii "Interferona bychyego rekombinantnogo" i "Tetravitferona-B"”, Regulatory issues in veterinary medicine num 2 (2018): 98-103; R. Iu. Khabriev, Rukovodstvo po eksperimentalnomu (doklinicheskomu) izucheniyu novykh farmakologicheskikh veshchestv (Moscow: Meditsina, 2005) y D. S. Maggs, “Antivirial therapy for feline herpesvirus infections”, Vet. Clin. North Amer. Small Anim. Pract num 40 (2010): 1055-1062.

[3] N. V. Danilevskaya; A. A. Deltsov y A. A. Antipov, “Bezopasnost preparata "Ribafloks" pri primenenii krysam v rekomenduyemoy, pyatikratnoy i desyatikratnoy doce”, Sovremennyye farmako- i biopreparaty. Moscow State Academy of Veterinary Medicine and Biotechnology named after K.I. Skryabin num 5 (2014): 36-40 y T. I. Reshetnikova; A. I. Liubimov y T. G. Krylova, “Embriotoksichnost i teratogennyy effekt khimioterapevticheskogo protivovirusnogo preparata”, International Journal of Veterinary Medicine num 3 (2018): 51-57.

[4] O. Yu. Rebrova, Statisticheskiy analiz meditsinskikh dannykh. Primeneniye paketa prikladnykh programm STATISTICA (Moscow: MediaSfera, 2002) y I. M. Rosliy y M. G. Vodolazhskaya, Pravila chteniya biokhimicheskogo analiza (Moscow: Medical Information Agency, 2010).

Materials and Methods

The experiment was carried out in the period from 2014 to 2018 based on the vivarium of the Department of Physiology and Pet Hygiene of the Faculty of Veterinary Medicine and the Interfaculty Educational and Scientific Laboratory of Biotechnology of the Federal State Budgetary Institution of Higher Education Izhevsk State Agricultural Academy (FSBEI HE Izhevsk State Agricultural Academy). The work with animals was carried out as per general ethical principles of conducting animal experiments and the provisions of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes[5]. Outbred white mice were used as laboratory animals. They were kept in specialized cages with metal grates and automatic drinkers. Zootechnical microclimate parameters in the vivarium complied with the standards. The animals were kept and fed per the guidelines for the maintenance of laboratory animals in vivariums of research institutes and educational institutions[6].

During the experiment, one control and four experimental groups were formed based on analogues, five females and five males in each. Fifty mice weighing 25 g, aged 90 days were used for the experiments. The drugs were administered to the mice intragastrically, using a probe, previously diluted in 0.2 ml of saline. The drugs were administered to the experimental mice once a day, for 21 days. Slaughter by decapitation took place on day 22, and blood was drawn for laboratory tests (Table 1).

Group 1 was the control one, and 0.2 ml of pure saline were administered to this group of animals.

The Triazavirin antiviral drug at a dose of 1 g per mouse weighing 25 g was administered to Group 2.

The Ingavirin antiviral drug at a dose of 0.12 mg per mouse weighing 25 g was administered to Group 3.

The Rimantadine antiviral drug at a dose of 0.24 mg per mouse weighing 25 g was administered to Group 4.

The Moxifloxacin antiviral drug at a dose of 0.5 mg per mouse weighing 25 g was administered to Group 5 (Table 1).

Experiment No.	**Drug**	**Number of animals**	**Dose, method, and mode of administration**
1	Control	10 mice (5 males and 5 females)	0.2 ml saline
2	Triazavirin	10 mice (5 males and 5 females)	1 g per animal
3	Ingavirin	10 mice (5 males and 5 females)	0.12 mg per animal
4	Rimantadine	10 mice	0.24 mg per animal

[5] European Convention for the Protection of Vertebrate Animals for Experimental and Other Scientific Purposes (Strasbourg: Council of Europe, 18 March 1986).

[6] European Convention for the Protection of Vertebrate… y H. J. Hedririch y G. Bullock. The laboratory mouse (Amsterdam: Elsevier Academic Press, 2004).

		(5 males and 5 females)	
5	Moxifloxacin	10 mice (5 males and 5 females)	0.5 mg per animal

Table 1
Design of the experiment

During the experiment, laboratory blood tests were performed.

Hematological studies were performed on the automatic Mindray BC-2800Vet hematology analyzer (PRC).

Biochemical studies were carried out on the LABIO-300 automatic biochemical analyzer (China).

Hormone levels were determined on the Alisei automated immunoassay analyzer (SEAC srl, Italy), ELISA (enzyme-linked immunosorbent assay) kits produced by Alcor Bio Company (Russia, St. Petersburg) were used for quantitative measurement of TSH, triiodothyronine (T_3), free thyroxine (T_4), cortisol.

The results were statistically processed through the variation statistics method using the Student's t-criterion. The data were presented as mean value ± standard error of the mean. The calculations were made on a personal computer using Microsoft Excel 7.0 as a statistical analysis program[7].

Results

The results of hematological, biochemical, hormonal studies of blood serum were obtained from the experimental use of some antiviral and antibacterial drugs in laboratory mice.

After administering Triazavirin for 21 days, a change was observed in the hematological parameters of blood serum, compared with the control group, as follows: leukocytes increased by 50.15 %, lymphocytes – by 10.96 %, platelets – by 37.65 %, monocytes decreased by 15.1 %, granulocytes – by 14.5 %, and hemoglobin – by 11.2 %.

When administering Ingavirin as per this scheme, the maximum increase in the leukocytes level by 183.5 % was noted in terms of the indicators in the control group. The level of monocytes also increased by 27.2 %, and the number of granulocytes decreased by 9.7 %, of hematocrit – by 9.2 %, and of platelets – by 5.8 %.

The injection of Rimantadine into the body of the mice caused minimal hematological fluctuations in blood serum parameters; in particular, the number of leukocytes increased by 143.7 %, of monocytes – by 6.6 %, platelet count decreased by 7.1 %, and hematocrit – by 8 %.

The experimental administration of the Moxifloxacin antibacterial drug for comparison with antiviral drugs showed an increase in leukocytes by 54.8 %, in lymphocytes – by 21.3 %, and a decrease in the level of monocytes by 28.7 %, and granulocytes – by 27.9 % (Table 2).

[7] O. Yu. Rebrova, Statisticheskiy analiz meditsinskikh dannykh. Primeneniye paketa prikladnykh programm STATISTICA (Moscow: MediaSfera, 2002).

Indicator	**Group 1**	**Group 2**	**Group 3**	**Group 4**	**Group 5**
	Control	**Triazavirin**	**Ingavirin**	**Rimantadine**	**Moxifloxacin**
Leukocytes, $*10^9$/l	6.58 ± 0.607874	9.88 ± 0.56839***	18.65714 ± 4.6**	16.0375 ± 3.519**	10.18889 ± 1.1795**
Lymphocytes, %	57.057 ± 2.335047	63.31 ± 1.938983*	59.44286 ± 3.708861	58.35 ± 3.954338	69.22222 ± 2.258***
Monocytes, %	5.3 ± 0.3106	4.5 ± 0.052**	6.742857 ± 0.151***	5.65 ± 0.804008	3.777778 ± 0.2446***
Granulocytes, %	37.4555 ± 2.00909	32.03 ± 1.766921**	33.81429 ± 2.833761	36 ± 3.179173	27 ± 3.773*
Red blood cells, $*10^{12}$/l	9.52 ± 0.03	9.1 ± 0.12155**	9.088571 ± 0.1738*	9.12 ± 0.193*	9.441667 ± 0.0013**
Hemoglobin, g/l	134.548 ± 6.9	119.509 ± 0.09*	138.3333 ± 6.936217	138 ± 2.60494	131.7143 ± 9.455949
Hematocrit, %	49.5 ± 0.4	46.57 ± 1**	44.92857 ± 1.3487**	45.55 ± 1.43**	47.6 ± 0.53**
Platelets, $*10^9$ l	752.5 ± 61.2	1035.8 ± 129*	708.2857 ± 44.11064	698.875 ± 66.87046	732.3333 ± 160.9424

Note: * – P ≥ 0.950, ** – P ≥ 0.990, *** – P ≥ 0.999

Table 2

Hematological blood parameters of the mice in the experimental and control groups

The intragastric administration of Triazavirin to the experimental mice causes changes in blood serum biochemical parameters. There is an increase in the level of globulins by 108.6 %, total protein – by 37.5 %, creatinine – by 15 %, and urea – by 36.5 %. There is a reduction in a number of indicators, as follows: AST – by 18.2 %, ALT – by 33.4 %, and the albumin-globulin ratio – by 56 %.

When studying the results of the experimental administration of Ingavirin, an increase in creatinine was found to be 43.3 %, in AST – 150.4 %, in ALP – 103.8 %, reduction of cholesterol – 43.7 %, of total protein – 5.8 %, and of ALT – 25.8 %.

In the experimental group of the mice that received Rimantadine, blood serum biochemical parameters varied and exceeded the level of the control group as follows: creatinine – by 133.1 %, AST – by 281.7 %, and ALP – by 226.8 %. The number of indicators decreased compared with the control, as follows: cholesterol – by 44.85 %, total protein – by 9.5 %, and ALT – by 16.86 %.

The use of Moxifloxacin led to an increase in total protein by 119.1 %, globulins – by 153.7 %, creatinine – by 165.99 %, urea – by 132.3 %, and a decrease in the albumin-globulin ratio by 42 %, and AST – by 31.69 % (Table 3).

Indicator	**Group 1**	**Group 2**	**Group 3**	**Group 4**	**Group 5**
	Control	**Triazavirin**	**Ingavirin**	**Rimantadine**	**Moxifloxacin**
Cholesterol, mmol/L	3.4 ± 0.05	3.5 ± 0.005*	1.914286 ± 0.4375***	1.875 ± 0.3151***	3.512 ± 0.0051*
Total protein, g/l	62.52 ± 1.6	85.96 ± 10.24*	58.88571 ± 0.15*	56.55 ± 1.6**	74.46 ± 3.524**
Albumin, g/l	34.98 ± 0.5	28.52 ± 1.7***	33.8 ± 0.149*	32.3625 ± 0.7599**	32.14 ± 0.8795**

Globulins, g/l	27.54 ± 1.833951	57.44 ± 10.4**	25.08571 ± 1.177655	24.1875 ± 1.214707	42.32 ± 3.373***
Albumin-Globulin Ratio	1.3255 ± 0.092444	0.584 ± 0.35*	1.372857 ± 0.095487	1.375 ± 0.1129	0.77 ± 0.05999***
Creatinine, μmol/l	20.604 ± 0.836882	23.7 ± 1.29*	29.57143 ± 2.4019***	27.42857 ± 1.721***	34.2 ± 5**
AST, u/l	71.76 ± 4.114	58.7 ± 1.0**	179.7143 ± 28.69***	202.125 ± 32.98***	49.02 ± 4.992***
ALT, u/l	30.22 ± 2.5	20.14 ± 3.276*	22.42857 ± 2.6677*	25.125 ± 0.1*	33.82 ± 7.58422
Urea, mmol/l	5.2 ± 0.4358	7.1 ± 0.675*	4.057143 ± 0.346999*	4.957143 ± 0.413382	6.88 ± 0.708*
ALP, u/l	97.3 ± 18.86478	50.14 ± 13.6*	198.2857 ± 2.763**	220.7143 ± 19.04**	49.28 ± 14.5*

Note: * – P ≥ 0.950, ** – P ≥ 0.990, *** – P ≥ 0.999

Table 3

Biochemical parameters of blood serum of the mice in the experimental and control groups

The analysis of the hormonal status of the mice showed that the use of Triazavirin led to a decrease in T_4 by 58.6 %, and T_3 – by 68.9 %. The use of Ingavirin lowers TSH by 70.5 % and increases T_3 by 221 %, and cortisol – by 646.6 %. Rimantadine, in turn, leads to a decrease in T_4 by 60 %, and to an increase in T_3 by 201 %, and in cortisol –by 574.9 %. Moxifloxacin inhibits the production of TSH by 82.4 %, and increases T_3 by 260.14 %, and cortisol – by 636.2 % (Table 4).

Indicator	**Group 1**	**Group 2**	**Group 3**	**Group 4**	**Group 5**
	Control	**Triazavirin**	**Ingavirin**	**Rimantadine**	**Moxifloxacin**
TSH, μme/ml	0.288 ± 0.102456	0.1128 ± 0.069106	0.085 ± 0.01*	0.12 ± 0.03	0.0508 ± 0.029*
T_4, pmol/l	12.63 ± 0.532718	5.23 ± 2.1***	8.055 ± 2.05*	5.05 ± 3.244*	7.9 ± 1.705**
T_3, nmol/l	1.43 ± 0.05164	0.445 ± 0.336**	3.16 ± 0.5038***	2.875 ± 0.51**	3.72 ± 0.7825**
Cortisol, nmol/l	24.36 ± 0.771607	60.76 ± 9.149***	157.5 ± 35.1***	140.05 ± 33***	154.98 ± 34.19***

Note: * – P ≥0.950, ** – P ≥ 0.990, *** – P ≥ 0.999

Table 4

The concentration of hormones in the blood serum of the mice in the experimental and control groups

Discussion

The analysis of the hematological parameters of the tested drugs has shown that leukocytes approach the upper limit of the standard only when Ingavirin is administered. The remaining indicators of white and red blood cells with significant fluctuations do not exceed the average permissible values.

When administering Triazavirin, the biochemical parameters are the most stable in comparison with other tested drugs, and only globulins and the total protein go beyond the average values.

Hyperproteinemia can be a consequence of dystrophic and inflammatory processes in the liver and in the body as a whole, including those caused by administering the drug.

When Ingavirin and Rimantadine are administered, cholesterol levels are significantly reduced, which negatively characterizes metabolic processes in the liver. Creatinine indicators increase, and those of urea – decrease, ALP tends to the upper limit of the average physiological standard.

The administration of Moxifloxacin increases the level of globulins, total protein, and creatinine, and reduces the rate of AST.

The activity of aminotransferases decreases, characterizing the absence of massive cytolysis of the liver cells and biliary dyskinesia. The deamination and transamination of amino acids are within the species norm.

The content of uric acid in blood serum decreases, indicating a slowdown in the urea formation function of the liver and a sparing mode of use of nucleic acids by the body for energy purposes.

Creatinine level increases, indicating an increase in protein metabolism.

Conclusion

1. With the experimental use of the above drugs, the Triazavirin test drug has positively proved itself. Triazavirin is safe and does not cause changes in white and red blood cells.

2. When using Triazavirin, the biochemical blood parameters are within the species physiological range. The ALT and ALP level decreases, cholesterol corresponds to the control. Globulins and total protein go beyond the average. The increase in the globulins testifies to the intensification of the body's immune defense factors.

3. The use of Triazavirin significantly influences the hypothalamic-pituitary system. The TSH is maintained within the average range, and the thyroid synthesis of the T_3 and T_4 is significantly reduced.

4. The use of Triazavirin causes stress in the experimental animals, resulting in a change in cortisol levels.

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