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STUDY OF HEMATOLOGICAL PARAMETERS OF RATS AT THE ACTION OF THE IMMUNOSTIMULATING DRUG «FLAVOVIR»

In the conducted research are studied hematologic indicators of blood of rats at effect of "Flavovir" immunoperformance-enhancing drug. It is established that medicine "Flavovir" in a dose of 35 mg/kg at single application causes statistically reliable (P≤0,001) increase of level of leukocytes, erythrocytes, hemoglobin and hematocrit. Against the background of statistically reliable (P≤0,001) decrease in level the polymorphonuclear neutrophils, a rise in lymphocytes. Oral introduction of the medicine "Flavovir" stimulates growth of leukocytes 6 days for 60% in a dose of 35 mg/kg, erythrocytes for 33%, hemoglobin to 159,12 ± 0,89g/l, the hematocrit to 52,25 ± 1,76%, lymphocytes on 2,3 times. Level of platelets increases to 838,00 ± 7,56×10^9/l (P≤0,001) and increase in percentage of eosinophils for 50% (P≤0,001) compared with control animals. Throughout an experiment change of body weight of rats of rather background values in one of the compared groups was not revealed. Change of water consumption in groups of the animals receiving the studied medicines concerning monitoring was not noted. Comparison of data of measurement of rectal temperature did not reveal reliable differences between experienced and control group of animals. Results of the pilot studies showed that existence of the accruing lymphocytosis can demonstrate activation of a cell-like link of immune system, that is the immunostimulating property of medicine.

Key words: immunostimulating drug, «Flavovir», hematological blood counts, rat, experiment.

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Иммунды ынталандырғыш «Флавовир» препаратының егеуқұйрықтардың гематологиялық көрсеткіштеріне әсерін зерттеу

Жүргізілген зерттеу жұмысы бойынша егеуқұйрықтардың гематологиялық көрсеткіштеріне иммунды ынталандырушы «Флавовир» препаратының 35 мг/кг дозасындағы әсері зерттелді. «Флавовир» препараттың 35 мг/кг дозасының бір реттік әсерінде жалпы лейкоциттер саны және

гематокриттің артуы байқалды. “Флавовир” 35 мг/кг концентрациясында 6 күн бойы әсерінде лейкоциттердің 60% өсуін ынталандырады, сондай-ақ эритроциттердің 33%, гемоглобиннің 159,12 ± 0,89 г/л, гематокриттің 52,25 ± 1,76% салыстырмалы түрде артулары байқалды. Полиморфоядролық нейтрофильдердің статистикалық тұрғыдан (P≤0,001) төмендеуінің фонында лимфоциттер саны 2,3 есеге артты. Тромбоциттер деңгейі 838,00 ± 7,56×10⁹/л (P≤0,001) артты және бақылау тобының жануарларымен салыстырғанда эозинофилдердің пайыздық көрсеткіштері 50% (P < 0,001) артып, шамалы эозинофилия байқалды. Эксперимент кезінде егеуқұйрықтардың тамақтану рационына препаратты қосып беру кезінде, препарат жануарлардың денсаулығына және жалпы жағдайларына теріс әсерлерін байқатқан жоқ және олардың жалпы дене салмақтарына оң әсерінде өсу қарқындылығының арттыруына мүмкіндік беріп артуы байқалды. Жануарлардың ректалды температураларын өлшеу кезінде бақылау тобымен және эксперименттік топтарын салыстырғанда сенімділік бойынша өзгерістері байқалған жоқ. Эксперименттік зерттеулердің нәтижелері бойынша гематологиялық көрсеткіштерде үдемелі лимфоцитоздың байқалуы иммундық жүйеде клеткалар буынының белсендірілуінің айғағы болып табылады, яғни препараттың иммунды ынталандырғыш қасиетке ие екендігін байқатты.

Түйін сөздер: иммунды ынталандырғыш препарат, «Флавовир», қанның гематологиялық анализі, егеуқұйрық, эксперимент.

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Исследование гематологических показателей крыс при действии иммуностимулирующего препарата «Флавовир»

В проведенном исследовании изучены гематологические показатели крови крыс при действии иммуностимулирующего препарата «Флавовир». Установлено, что препарат «Флавовир» в дозе 35 мг/кг при разовом применении вызывает статистически достоверное (P≤0,001) возрастание уровня лейкоцитов, эритроцитов, гемоглобина и гематокрита. На фоне статистически достоверного (P≤0,001) снижения уровня полиморфноядерных нейтрофилов отмечено нарастание лимфоцитов. Пероральное введение препарата «Флавовир» в дозе 35 мг/кг стимулирует рост лейкоцитов к 6 суткам на 60%, эритроцитов на 33%, гемоглобина до 159,12 ± 0,89г/л, гематокрита до 52,25 ± 1,76%, лимфоцитов в 2,3 раза. Уровень тромбоцитов возрастает до 838,00 ± 7,56×10⁹/л (P≤0,001) и отмечено повышение процентного содержания эозинофилов на 50% (P≤0,001) по сравнению с контрольными животными. На протяжении эксперимента не было обнаружено изменения массы тела крыс относительно фоновых значений ни в одной из сравниваемых групп. Не отмечалось изменения потребления воды в группах животных, получавших исследуемые препараты, относительно контроля. Сравнение данных измерения ректальной температуры не выявило достоверных различий между опытной и контрольной группами животных. Результаты экспериментальных исследований показали, что наличие нарастающего лимфоцитоза может свидетельствовать об активации клеточного звена иммунной системы, то есть иммуностимулирующем свойстве препарата.

Ключевые слова: иммуностимулирующий препарат, «Флавовир», гематологический анализ крови, крыса, эксперимент.

Introduction

At present, certain changes in the environment are observed in Kazakhstan. Adverse factors accrue (both ecological, and social), living conditions of separate groups of the population (especially in regions and rural areas), quality of atmospheric air, food, drinking water worsen. All these factors have negative effect on the immune status of the person and lead to developing of diseases (Bajdaulet, 2013: 64; Klimov, 2006:122).

Therefore, restoration of immunological violations – a relevant task as the majority of chronic, somatic, infectious diseases is followed by secondary

immunological insufficiency. Algorithmization of immunocorrection (immunomodulation) assumes use of pharmacological means which are capable to increase (immunostimulation) or to reduce (immunosupression) the level of the immune answer (Abramov, 1991:45; Pastushenkov, 1995: 68; Haitov, 2003:196).

Therapy by medicines of natural origin is widely used in world medical practice. Phytomedicines find application for treatment and prevention and also in complex therapy of various diseases (Avdeeva, 2007:26; Tuzankina, 2010:485). Often they are used without appointment of the doctor, at the same time patients risk to exceed the established therapeutic doses up to emergence of side effects. Therefore studying of toxicity of medicine of a phytogenesis is necessary at a stage of preclinical assessment.

The immune system performs the important function on maintaining constancy of the internal environment of an organism which is carried out by recognition and elimination from an organism of alien substances of the anti-gene nature (Jieldanjwski, 1983:349; Hoffman, 1989:1371; Nores, 1997:99). Now a big problem of applied medicine is increase in number of diseases which cornerstone immunopathological processes are (Sanz, 2009:1909; Shivaprasad, 2006:32). Opportunity and consequences of infection of a human body with causative agents of infectious diseases depend on a condition of immune system, in particular. Violations in the immune answer usually promote synchronization of infectious process and development of complications (Esimova, 2012:93; Sablin, 2012:18). Besides, the number of strains of microorganisms, resistant to antimicrobial therapy, increases every year (Chereshnev, 2014:120).

The problem of immunocorrection of the broken homeostasis is a current problem in clinical practice. It includes as search, creation of effective immunocorrective remedies and also development of effective methods of immunodiagnostics and treatment. The relevance of a pharmakokorrektion of immunological insufficiency, first of all, is caused by wide circulation of immunodeficiency at the people who are the reason of various diseases which success of treatment in many respects depends on the choice of adequate means and methods of immunocorrection. It is known that many factors and influences have immunosuppressive property: stresses, bacteria and viruses, toxic substances, the ionizing radiation (Jiang, 2012:40). The strategy of modern scientific research in this course first of all is directed to detailed studying of mechanisms of an immunosuppression and the search of effective remedies of correction broken immune a homeostasis. All these aspects dictate need of use the immunotropic of medicines that allows to constrain distribution of multiple medicinal stability of microorganisms and to try to obtain treatment of patients with insufficiency of the immune answer (Hobrakova, 2008:324; Haring, 2005:3855).

Now the pharmaceutical market offers various medicines. Most of them are synthetic and quite often cause complications, including aggravation the immunosuppressive of states, pollute raw materials and food, the environment. This circumstance causes need of further development and deployment in clinical practice of medicines of natural origin which are deprived of the specified shortcomings and they can be applied as separately, and in a complex with other means. Most of these drugs have a number of advantages over synthetic drugs: multifaceted effects on the body, immunomodulatory effect, low toxicity, activation of the functions of the neuroendocrine system, stimulation of regeneration processes, weakening of stress factors, increase of immune response during vaccination, reduction of the use of chemotherapeutic agents and increase their therapeutic effect (White, 2008:1789; Geha, 2007:776).

One of the most promising sources of phytopreparations are medicinal plants containing flavonoids, which, due to their wide distribution in plants and large structural diversity, are currently the focus of researchers in the fields of pharmacognosy, pharmacy and medicine. Flavonoids – the most numerous class of natural phenolic connections of which the structural variety, high and versatile activity and small toxicity is characteristic (Spalatin, 1970:542). Wide amplitude of biological activity of flavonoids is connected with variety of their chemical structures and various physical and chemical properties following from them. This interest is connected with that circumstance that flavonoids, being evolutionarily adequate to a human body, cause antioxidant, antiviral, angioprotective, hepatoprotective, bile-expelling, diuretic, neurotropic and other major pharmacological properties. And above-mentioned pharmacological effects most involve scientists in the field of creation of new vegetable medicines (Duran, 2002:338). Despite some study of a problem of use of medicines of natural origin with the immunostimulating activity, many aspects of their clinical use demand further development, justification and introduction in clinical practice. For the correction of immunodeficiency states, complex plant preparations with certain directionality of action

should be used. Therefore development of effective complexes on the basis of biologically active agents of the plants possessing immunomodulatory and other properties for prevention and treatment of immunodeficiency is a relevant problem of modern science.

The purpose of researches was: evaluation of the effect of the drug "Flavour" on hematological parameters and the dynamics of weight changes of albino rats in the preclinical studies in experimental conditions.

Materials and Methods

Experiments were made on 15 not purebred white rats males weighing 220-230 g. Animals of the first group served as control and did not apply any medicines (intact animals). Animals of the second and third group – skilled also received in addition with a forage nutritional supplement of plant origin of Flavovir in a dose of 35 mg/kg, the second group – 1 day, and the third group the same doses (35 mg/kg) within 6 days. The basic rules of maintenance and care were in accordance with the data standards (Bettstetter, 2003:68). Throughout an experiment noted dynamics of body weight. The general condition was estimated at daily survey of animals. For the 7th days of rats hammered and carried out an intake of peripheral blood.

The blood of experimental animals was collected in a vacuum blood with anticoagulants, it is tenfold mixed for an exception of formation of microclots and brought to laboratory. To assess hematological parameters, a general blood test was performed on the automatic hematological analyzer Siemens ADVIA 2120 (Germany).

Used the following indicators: WBC – Leukocytes (absolute quantity), RBC – Erythrocytes (absolute quantity), HGB – Hemoglobin (concentration), HCT – Hematocrit (percent), MCV – the Average volume of erythrocytes, MCH – the Average content of hemoglobin in a separate erythrocyte, MCHC – Average concentration of hemoglobin in the eritrotsitarny weight, RDW – Width of distribution of erythrocytes, PLT – Platelets (absolute), MPV – the Average volume of platelets, % NEUTRO – Neutrophils (relative a stake.), NEUTRO abs – Neutrophils (absolute a stake.), % LYMPHO – Lymphocytes (relative a stake.), LYMPHO abs – Lymphocytes (absolute a stake.), MONO of % – Monocytes (relative a stake.), MONO abs – Monocytes (absolute a stake.), BASO of % – Basophiles (relative a stake.), BASO abs – Basophiles (absolute quantity), EOS of % – Eosinophils (relative a stake.), EOS abs – Eosinophils (absolute quantity).

Statistical data processing was carried out with determination of average value, a mean square and standard deviation, statistical error of average and percent of distinctions. In determining the reliability of the difference between the indices of the compared groups, the reliability t-criterion was calculated, the value of P was determined from the Student's table, the changes were considered reliable at $p \leq 0{,}001$. All data have been calculated in the software package of MS Offis Excel.

Results and Discussion

For studying nutritional supplement of plant origin of Flavovir in a dose of 35 mg/kg have been analysed hemocytogram of experimental animals (table 1).

According to table 1, at a dosage of the medicine «Flavovir» the total number of leukocytes in the second group statistically authentically increased in concentration of 35 mg/kg with $7{,}33 \pm 0{,}08 \times 10^9$/l to $8{,}34 \pm 0{,}15 \times 10^9$/l, the total number of erythrocytes significantly didn't change, and concentration of hemoglobin remained within norm, reliable increase of level of the hematokrit to 46,65±1,27% is noted statitsichesk.

The average volume of an erythrocyte, average content of hemoglobin in a separate erythrocyte, average concentration of hemoglobin in erythrocyte weight, the settlement width of distribution of erythrocytes on volume, the total number and average volume of platelets remained within physiological norm. The percentage of neutrophils also statistically authentically decreased from 21,74±0,46% to 17,10±0,21%. At the same time the percentage of lymphocytes has statistically authentically increased to 79,03±0,07%. Level of basophiles and quantity of eosinophils practically didn't change. Thus, analyzing hematologic indicators of experimental animals against the background of single reception nutritional supplement of a phytogenesis "Flavovir" it is revealed what in a dosage of 35 mg/kg causes statistically reliable increase of total number of leukocytes for 15% and the gematokrit for 11%. It should be noted what against the background of statistically reliable decrease in level the polymorphonuclear of neutrophils, in turn the level of lymphocytes statistically increased for 94% that can demonstrate activation of a cellular link of immune system.

Table 1 – Hematologic indicators of rats against the background of a dosage Flavovir of 35 mg/kg

Indicators	Internatio-nal name	Control	1 day	6 days
Total number of leukocytes, $\times 10^9$/l	WBC	7,33±0,08	8,34±0,15*	11,69±0,28*
Total number of erythrocytes, $\times 10^{12}$/l	RBC	6,99±0,24	7,02±0,32	9,27±0,27*
Concentration of hemoglobin, g/l	HGB	139,92±1,67	143,52±1,68	159,12±0,89*
Hematocrit indicator, %	HCT	41,95±1,76	46,65±1,27*	52,25±1,76*
Average volume of an erythrocyte, fl	MCV	68,25±0,34	69,07±0,37	68,97±0,68
The average content of hemoglobin in a separate erythrocyte, fl	MCH	18,48±0,17	18,85±0,20	19,29±0,18*
Average concentration of hemoglobin in erythrocytes weight, g/l	MCHC	298,91±3,38	299,21±2,91	299,71±1,23
Settlement width of distribution of erythrocytes on volume, %	RDW	13,39±0,24	13,69±0,18	13,93±0,17
Total number of platelets, $\times 10^9$/l	PLT	751,80±9,35	755,80±6,14	838,00±7,56*
Average volume of platelets, fl	MPV	6,64±0,18	6,69±0,12	7,16±0,12*
Percentage of neutrophils, %	NEUTRO %	21,74±0,46	17,10±0,21*	14,96±0,10*
Absolute quantity of neutrophils, $\times 10^9$/l	NEUTRO abs	0,55±0,01	0,43±0,01*	0,37±0,02*
Percentage of lymphocytes, %	LYMPHO %	40,70±0,46	79,03±0,07*	92,00±0,06*
Absolute quantity of lymphocytes, $\times 10^9$/l	LYMPHO abs	2,50±0,06	3,27±0,08*	4,48±0,06*
Percentage of monocytes, %	MONO%	28,05±0,34	29,79±0,55*	30,38±0,35*
Absolute quantity of monocytes, $\times 10^9$/l	MONO abs	3,56±0,27	4,16±0,33	4,04±0,26
Percentage of basophiles, %	BASO %	0,21±0,10	0,28±0,02	0,23±0,12
Absolute quantity of basophiles, $\times 10^9$/л	BASO abs	0,12±0,07	0,15±0,08	0,13±0,04
Percentage of eosinophils, %	EOS %	0,93±0,12	0,94±0,04	1,40±0,03*
Absolute quantity of eosinophils, $\times 10^9$/l	EOS abs	0,10±0,05	0,11±0,04	0,22±0,04
Note: * statistically authentically in relation to control (P≤0,001)				

The analysis of the results presented in table 1 "Flavovir" of 35 mg/kg within 6 days reflects indicators of a hemotsitogramma of experimental rats against the background of a dosage. Statistically reliable increase in total number of leukocytes with 7,33±0,08×10^9/l to 11,69±0,28×10^9/l was observed, the total number of erythrocytes increased to 9,27±0,27×10^9/l, hemoglobin up to 159,12±0,89 g/l, hematocrit up to 52,25±1,76%. Erythrocyte coefficients significantly didn't change during all experiment, including the average volume of an erythrocyte, average content of hemoglobin in a separate erythrocyte, average concentration of hemoglobin in erythrocyte weight, the settlement width of distribution of erythrocytes on volume. Total number of platelets statistically authentically changed towards increase, but nevertheless remained within physiological norm.

On indicators of white blood it should be noted that the percentage of neutrophils statistically authentically decreased with 21,74±0,46×10^9/l to 14,96±0,10×10^9/l. The maximum increase of lymphocytes to 92,00±0,06% respectively is noted. The percentage of basophiles significantly didn't change, but the level of eosinophils has statistically authentically increased from 0,93±0,12 up to 1,59±0,25%, and in absolute values with 0,10±0,05×10^9/l to 0,22±0,04×10^9/l (P≤0,001).

Thus, in the third test group with drug application "Flavovir" at a concentration of 35 mg / kg of total leukocytes significantly increased by 60%, the percentage of neutrophils statistically reduced by 45%. There was increase in the percentage of eosinophils by 50%, a slight eosinophilia. Also, use of the drug leads to a relative increase of 33% red blood cells, hemoglobin up to 159,12 ± 0,89 g/l, hematocrit up to 52,25 ± 1,76% red blood counts in this case indicate better Pereni drug concentration in 35 mg/kg, as well as possibly the inclusion and the absence of compensatory mechanisms dehydration experimental animals.

The total number of platelets was growing, that may be due not only to the Primus product, but also with the physiological biological cycles in experimental animals. The maximum increase in

lymphocytes was observed 2.3 times. The presence of lymphocytes, may indicate the activation of the cellular system of the immune system, that is, the immunostimulating property of the drug (Haitov, 2005:30; Petenkova, 2011:66; Ablajhanova, 2016:104).

Table 2 – Dynamics of live mass of animals at inclusion in a diet Flavovir nutritional supplement in a dose of 35 mg/kg, n=5 (M±m)

Indicators	Control	II experimental group (1 day)	III experimental group (6 days)
Before the experiment	223,40±4,32	225,60±4,32	224,40±4,32
After the experiment	228,80±4,79	231,40±4,22	233,20±4,87
Difference in weight in comparison with an initial state, %	+ 2%	+ 2,6%	+ 3,9%

One of the most important indicators of efficiency of nutritional supplement is her influence on intensity of growth. The data of Table 2 show that at the beginning of the experiment the rats had approximately the same mass, the difference between them was insignificant. The study found that the experimental rats looked healthy, had a good appetite, there were no deviations in clinical status and behavior.

In the third skilled Flavovir group has exerted positive impact on an organism of animals. So, use of medicine promoted her increase, at the end of the experimental period the mass of animals exceeded initial values for 3,9%.

Thus, addition in a diet of rats Flavovir nutritional supplement in a dose of 35 mg/kg doesn't make negative impact on the general state and health, positively affects intensity of their growth.

Conclusion

As a result of the conducted scientific researches the following conclusions have been drawn:

1. At single use (1 day) of medicine "Flavovir" in a dose of 35 mg/kg causes statistically reliable increase of total number of leukocytes to 8,34±0,15×10^9/l and the hematokrit to 46,65±1,27%. Also use of medicine leads to statistically reduction contents the polymorphonuclear of neutrophils to 17,10±0,21% and to hobby the maintenance of lymphocytes up to 79,03±0,07%.

2. At use of the medicine, "Flavovir" within 6 days stimulates growth of leukocytes by 60% (P≤0,001) in concentration of 35 mg/kg. Also use of medicine leads to relative increase of erythrocytes for 33%, hemoglobin up to 159,12±0,89 g/l, hematocrit up to 52,25±1,76%. Against the background of statistically reliable (P≤0,001) decrease in level the polymorphonuclear of neutrophils, increase of lymphocytes on 2,3 times is noted. Level of platelets increases to 838,00 ±7,56×10^9/l (P≤0,001) and is noted increase in percentage of eosinophils for 50% (P ≤0,001) in comparison with control animals, an insignificant eosinophilia.

3. By results of experiences, inclusion in a diet of rats Flavovir nutritional supplement in a dose of 35 mg/kg of live weight doesn't make negative impact on the general state and health of rats, positively affects intensity of their growth, promotes increase in additional weights for 3,9 %.

Thus, as a result of the conducted researches, normative (reference) values for evaluation of extended hematological parameters of blood of outbred laboratory rats on the hematological analyzer Siemens ADVIA 2120 were obtained. And also according to experimental data, the presence of increasing lymphocytosis may indicate the activation of the cellular link of the immune system, that is, the immunostimulating property of drugs.

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