PRELIMINARY RESULTS OF THE RESEARCH OF THE EFFECTIVENESS OF THE DRUG DINO96 IN CLINICAL PRACTICE

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Annotation: The efficiency of the drug DINO96 as an independent biomarker and pharmacological test for non-invasive (AMP) diagnostics. Found that dermatologic phenomenon that appears when the drug DINO96 solution 0.2% applied to the skin surface has independent diagnostic value for screening and differential diagnosis of thyroid cancer, varicose veins and other diseases.

The possibilities of the use of diagnostic and therapeutic drug DINO96 are shown. First the possibility of non-invasive (AMP) diagnosis in vivo latent, early forms of violations of trace element, protein, carbohydrate, lipid, hormonal metabolism, cellular immunity, the hemostatic system was discovered. The forms of these disorders identified through pharmacological test which we developed for non-invasive (ILA) diagnostics. On the basis of non-invasive (AMP) diagnostics using pharmacological (DINO96) test set to the phenomenon of consumption for cellular and plasma factors of blood level and disclosed its diagnostic value:

1. for the cellular component of blood:
   - platelets;
   - red blood cells;
   - leukocytes;
   - neutrophils (segmented and stab)
   - lymphocytes;
   - eosinophils;

2. Plasma level of blood:
   - hypocalcemia consumption;
   - hypoproteinemia consumption;
   - hypofibrinogenemia consumption;
   - gipoglutamateminya consumption and others.

It is recommended for pharmacological tests to detect low-intensity chronic inflammation, susceptibility to hyper-coagulation and allergic diseases.

It is discovered the immunity modulating and anti-inflammatory drug.

Non-invasive (AMP) diagnostic method immunodeficiency states is proposed, in which the pharmacological test is DINO96.
We studied several aspects of the drug on the cardiovascular, nervous, system, liver and kidneys and justified some of the mechanisms of drug action on the human body after a single application DINO96.

Non-invasive (AMP) in the dynamics of complex diagnostic studies (pharmacological test DINO96) can be considered as a method to detect early, individual disorders of homeostasis of the human body, which has the world priority. Even one of the well-known methods of diagnosis, in vivo non-invasive, does not register 128 the vital signs of the human body. And even one of the known pharmacological tests (except DINO96) is not possible, without causing side effects or complications, diagnose, normal or abnormal (both latent and clinically expressed) homeostasis of the organism.

This comprehensive approach may be of great importance to detect early, before clinical disease, and for diagnosis and choice of treatment for many pathologies of organs and body systems. In terms of pharmacotherapy development of methods of treatment (DINO96) of varicose veins of the lower extremities, the method of complex treatment of varicose veins, the main product of the complex - DINO96.

The methods was tested on 63 patients with a positive effect. All patients received a consent form.

We are working on applications for 16 patents and 43 articles and six books. Among them, the monograph: "Diagnostic features and clinical application of pharmacological drug DINO96," "Disorders of calcium" and others. In a multi-volume guide for noninvasive (AMP) diagnosing a chapter will be devoted to "DINO96 as pharmacological test for non-invasive (AMP) diagnostics," etc.

The work is seen as an intermediate stage in the drug DINO96 into clinical practice. But today we can identify areas of possible use of the drug (in brief):

1. Allergy and Immunology (in vivo diagnosis and treatment of secondary immunodeficiency status).
2. Critical care medicine, oncology (DINO96 in combination with other drugs - nutritional support, it is designed for non-invasive monitoring);
3. Combustiology (burn surface treatment, nutritional support, correction of protein metabolism);
4. Surgery (preoperative, postoperative management of patients: treatment of the wound surfaces);
5. Urgent, first aid, self-help (burns, wounds - DINO96 in home and car kit).
6. urology;
7. Gastroenterology (erosion, ulcers);
8. Neurology (correction of metabolism, treatment of disorders of muscle tone of central origin, and so on.
9. Hematology, angiology
13. Pulmonology, Tuberculosis, and AIDS.

These data are preliminary, some aspects of the results need to be clarified and further research. DINO96 as pharmaceuticals, is perspective of diagnostic and clinical terms. Further studies are needed to examine the clinical value of the drug and generation methods of treating diseases.
Noninvasive (AMP) diagnosis of hypo-and Hyperproteinemia

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2013

Annotation: The study involved 65 patients with pathology of the gastrointestinal tract. Research results obtained with noninvasive analyzer AMP "BIOPROMIN" (Ukraine). The possibility of using the drug DINO96 tested for non-invasive (AMP) diagnosis of latent forms - latent gipoprotein-emii, hypoproteinemia consumption.

The human proteins form one of the most important groups of macromolecules. Body with mass of 70 kg contains about 10 kg of protein, most of them are localized in the muscles. In comparison with other proteins share nitrogenous substances in the body is low. Therefore, the nitrogen balance in the body is determined by the metabolism of proteins, IOM, which is regulated by several hormones, particularly testosterone and cortisol nom. [1]

Protein foods are a source of amino acids (for protein synthesis in the body) and energy. It is indispensable for human amino acids are threonine, valine, isoleucine, leucine, lysine, tryptophan, methionine, phenylalanine and histidine. The need for them is 250-1100 mg / day. Methionine and phenylalanine, respectively, can be synthesized from cysteine and tyrosine, which thus satisfy the need of this essential amino acid.

The need for protein depends on its biological value, which is primarily determined by the content of essential amino acids. Below are the basic foods in order of the biological value of proteins within them: animal products, legumes, grains (rice, wheat, maize), root vegetables.

The need for protein for adults are given in Table. 1 (0.6 g / kg), involves the use of animal products with high biological value. The lower the biological value of the protein, the greater the consumption.

The need for protein increases if insufficient intake of energy from non-protein sources. In this case, the amino acid foods are not used for protein synthesis, as well as a source of energy (gluconeogenesis or oxidation). Thus, inadequate energy intake predisposes to deficiency of protein, so protein-energy malnutrition is more common than an isolated deficiency of energy.
The need for protein increases as in the period of intensive growth, pregnancy and lactation, when resuming a normal diet after exhaustion and reduced hepatic failure and renal failure. In the first case, slowing the catabolism of amino acids (nonessential and essential), the second - the accumulating ammonia can be re-used for the synthesis of amino acids. In both cases, the portability of the protein is reduced, so that even the normal content in the diet can cause or exacerbate hepatic encephalopathy uremia. [2,3,4]

Nitrogen metabolism in general balance in healthy adults (the number of incoming and protein nitrogen excreted approximately equal.)

Table 1. Recommendations for pitaniyua [5]

<table>
<thead>
<tr>
<th>Category of persons</th>
<th>Age</th>
<th>Weight</th>
<th>Height</th>
<th>Proteins</th>
<th>Fat-soluble vitamins</th>
<th>Water-soluble vitamins</th>
<th>Minerals</th>
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</thead>
<tbody>
<tr>
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<td>1. 2. 3. 4. 5. 6. 7. 8. 9. 10. 11. 12. 13. 14. 15. 16. 17. 18.</td>
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<td>Children</td>
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<td>0-0.5</td>
<td>6</td>
<td>60</td>
<td>13</td>
<td>375</td>
<td>7.5 3 5 30 0.3 0.4 5 0.3 25 0.3</td>
<td>400 300 40 6 5 40 10</td>
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<tr>
<td>0.5-1</td>
<td>9</td>
<td>71</td>
<td>14</td>
<td>375 10 4 10 35 0.4 0.5 6 0.6 35 0.5</td>
<td>600 500 60 10 5 50 15</td>
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<tr>
<td>1-3</td>
<td>13</td>
<td>90</td>
<td>16</td>
<td>400 10 6 15 40 0.7 0.8 9 1.0 50 0.7</td>
<td>800 800 80 10 70 20 20</td>
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<tr>
<td>4-6</td>
<td>20</td>
<td>112</td>
<td>24</td>
<td>500 10 7 20 45 0.9 1.1 12 1.1 75 1.0</td>
<td>800 800 120 10 10 90 20</td>
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<td>7-10</td>
<td>28</td>
<td>132</td>
<td>28</td>
<td>700 10 7 30 45 1.0 1.2 13 1.4 100 1.4</td>
<td>800 800 170 10 10 120 30</td>
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<td>11-14</td>
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<td>157</td>
<td>45</td>
<td>1000 10 10 45 50 1.3 1.5 17 1.7 150 2.0</td>
<td>1200 1200 270 12 15 150 40</td>
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<td>15-18</td>
<td>66</td>
<td>176</td>
<td>59</td>
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<td>1200 1200 400 12 15 150 50</td>
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<td>19-24</td>
<td>72</td>
<td>177</td>
<td>58</td>
<td>1000 10 10 70 60 1.5 1.7 19 2.0 200 2.0</td>
<td>1200 1200 350 10 15 150 70</td>
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<td>25-50</td>
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<td>176</td>
<td>63</td>
<td>1000 5 10 80 60 1.5 1.7 19 2.0 200 2.0</td>
<td>800 800 350 10 15 150 70</td>
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<td>51 and older</td>
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<td>173</td>
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<td>800 800 350 10 15 150 70</td>
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<td>11—14</td>
<td>46</td>
<td>157</td>
<td>46</td>
<td>800 10 8 45 50 1.1 1.3 15 1.4 150 2.0</td>
<td>1200 1200 280 15 12 150 45</td>
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<td>15-18</td>
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<td>163</td>
<td>44</td>
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<td>1200 1200 300 15 12 150 50</td>
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<td>19-24</td>
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<td>51 and older</td>
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<td>800 5 8 65 60 1.0 1.2 13 1.6 180 2.0</td>
<td>800 800 280 10 12 150 55</td>
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<td>Pregnant</td>
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<td></td>
<td>60</td>
<td>800</td>
<td>10</td>
<td>10 65 70 1.5 1.6 17 2.2 400 2.2</td>
<td>1200 1200 320 30 15 175 65</td>
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<tr>
<td>Lactating period</td>
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<tr>
<td>First 6th months</td>
<td>65</td>
<td>1300</td>
<td>10</td>
<td>12 65 95 1.6 1.8 20 2.1 280 2.6</td>
<td>1200 1200 355 15 19 200 75</td>
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<td>Second 6th months</td>
<td>62</td>
<td>1200</td>
<td>10</td>
<td>11 65 90 1.6 1.7 20 2.1 260 2.6</td>
<td>1200 1200 340 15 16 200 75</td>
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</table>

Amino acids (free and composed of proteins) contain almost 95% of total nitrogen, so they cause and maintain nitrogen balance. Nitrogen balance - the difference between the amount of nitrogen from food, and the amount of nitrogen excreted (mostly in the form of urea and ammonium salts). If the quantity
supplied equals the number of nitrogen excreted, nitrogen equilibrium comes. Such a condition is a normal person with a normal diet. Nitrogen balance can be positive (N receives more than derived) in children and in patients recovering from severe illnesses. Negative nitrogen balance (nitrogen excretion predominates over his receipt) observed during aging, and starvation during severe illness. When there is a protein-free diet, nitrogen balance is negative. Compliance with this diet for a week leads to the fact that the amount of generated nitrogen ceases to increase and stabilize the value of about 4 g / day. This amount of nitrogen contained in 25 g of protein. Hence, for a day of protein deficit in the body consumes about 25 grams of protein own tissues. The minimum amount of protein in the diet, necessary to maintain nitrogen balance, corresponds 30-50 g / cyt, optimal same amount at an average exercise is about 100-120 g / day. [6] Stocks of protein in the human body is almost absent, and the new proteins can be synthesized only from amino acids coming from food and decaying tissue proteins. Of the substances that make up carbohydrates and fats, proteins are formed.

Lack of protein in the diet causes growth retardation in children and development, and in adults - a profound change in the liver, disruption of the endocrine glands, hormonal changes, it impaired nutrient absorption, can be problems with the heart muscle, impaired memory and performance. All this is due to the fact that the proteins are involved in almost all metabolic processes in the body. In the 70's there were deaths among people for a long time observing low-calorie diet with severe protein deficiency. This occurred because of serious violations in the heart muscle.

Protein deficiency reduces the body's resistance to infections, because it reduces the level of antibody formation. Disrupt the synthesis and other protective factors - lysozyme and interferon, which is why during the acute inflammatory process. In addition, protein deficiency is often accompanied by vitamin deficiency B12, A, D, K, and so on, which also impacts on health. They are part of enzymes that control the reactions and transamination dekarboksilirovaniya-amino acids, and play, respectively, an important role in the metabolism of amino acids (especially tryptophan), and protein metabolism in general, and in the metabolism of biogenic amines and neurotransmitters - serotonin, γ-aminobutyric acid, dopamine, norepinephrine, which determines the importance of this vitamin for the nervous system, and protein metabolism. Complete protein deficiency in the body can be detrimental for almost the entire body. With a shortage of protein digestion deteriorates some vitamins, fats, and many trace elements. Because hormones are protein structures, the lack of protein can lead to serious hormonal disorders-tion. Numerous studies have identified characteristic nedostaka certain amino acids of disability. If the diet is lacking tryptophan, isoleucine, methionine, or, in the liver decreases the formation of albumin and globulins, so that disrupts the formation of urine and water balance, edema, decreased antibody production. In rheumatoid arthritis in children [7], as well as toxemia of pregnancy in women [8] in the diet is usually detected pronounced deficiency of methionine. In animals with a deficit of tryptophan or methionine fall coat, and with a lack of histidine, phenylalanine and other amino acids, redness eye cataract. It was shown that with a lack of arginine in animals deteriorating quality and reduced sperm production [9], which can cause sterility of males, and the deficit of tryptophan atrophy of the testes in males and miscarriage in females. Methionine deficiency either in animals or in humans, can cause fatty liver. At the same time, to maintain the normal functioning of the protein metabolism requires all amino acids.

Any physical activity is harmful muscle cells, and the larger the load, the more damage it causes the muscles. To repair damaged muscle cells must have enough quality protein. The beneficial effects of physical activity on health status can occur only at sufficiently rated protein comes from food.

Most patients with tumors characterized by progressive siruyuschaya weight loss, and with it, and protein.
Cachexia occurs in 5-25% of patients with oncologic, while in 45% of hospitalized patients experienced weight loss. The term "cancer cachexia" describes a group of symptoms and syndromes characteristic of patients with metastatic disease, but occurs in patients with local tumor process. It is known that the amount of tumor is not a measure of cachexia. Most important is the localization of tumors, especially in lesions of the gastrointestinal tract.

Table 2. Metabolic disorders in cancer patients. [16]

<table>
<thead>
<tr>
<th>kind of metabolism</th>
<th>metabolic disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>The energy consumption</td>
<td>A moderate increase in many tumors</td>
</tr>
<tr>
<td>glycometabolism</td>
<td>Impaired glucose tolerance&lt;br&gt;Elevated / normal fasting glucose&lt;br&gt;Normal / reduced levels of insulin&lt;br&gt;Reduction of response to insulin&lt;br&gt;Increased gluconeogenesis from alanine, lactate and glycerol&lt;br&gt;Increased production and turnover of glucose</td>
</tr>
<tr>
<td>fat metabolism</td>
<td>Depletion of fat reserves&lt;br&gt;hyperlipidemia&lt;br&gt;increase lipolysis&lt;br&gt;decrease lipogenesis&lt;br&gt;Increased exchange neessentialsialnyh fatty acids and glycerol&lt;br&gt;The lack of glucose to suppress the oxidation of fatty acids neessentialsialnyh&lt;br&gt;Reducing lipoprotein lipase in plasma</td>
</tr>
<tr>
<td>protein metabolism</td>
<td>Increased protein metabolism&lt;br&gt;Reduction of protein synthesis and increased catabolism of muscle&lt;br&gt;Increased protein synthesis in the liver</td>
</tr>
</tbody>
</table>

Cachexia syndrome is characterized by various pathological conditions such as cancer, sepsis, chronic obstructive pulmonary disease and chronic heart failure. [10] It is believed that 50-80% of cancer patients in varying degrees, suffer from the symptoms of cancer cachexia. [11] Traditionally defined as a comprehensive cachexia syndrome: a patient snizhetsya weight, having anorexia, early feeling of saturation, there hemosen-weed violations, signs of systemic inflammation, hypermetabolism, and a number of other factors that lead to malnutrition, anemia, poor tolerability and low effectiveness of therapy, worsening quality of life and death. [12]

In accordance with the international consensus cancer cachexia is usually determined as a complex syndrome that is characterized by progressive decline in skeletal muscle mass (may be accompanied or not accompanied by a loss of fat mass) and the growth of functional impairment that can not be fully cropped during standard nutritional support.

There are three stages of the process: prekaheksiyu, cachexia and refractory cachexia. In the first stage (prekaheksiya) occur early clinical and laboratory signs of exhaustion (eg, anorexia, impaired glucose tolerance, etc.) with no significant decrease in body weight. Weight loss of 5% or more of a constant in the last 6 months or its progressive decline of 2% or more from baseline in body mass index (BMI) ≤ 20 kg/m²,
or the presence of sarcopenia and weight loss for 2% or more of the original can diagnose cachexia. Signs refractory cachexia arises against far-gone or rapidly progressing cancer process are poor functional status of the patient’s lack of response or intolerance to anti-tumor therapy and treatment to correct body weight, life expectancy of less than 3 months. [13]

Leading components of cancer cachexia, requiring diagnostic evaluation, recognized anorexia and reduced food consumption, the prevalence of catabolic processes in the body, decrease in muscle mass and strength (sarcopenia), deterioration of functional status and quality of life. Sarcopenia is defined as a condition in which the patient’s skeletal muscle mass in the range of ≤ 5 percentile of the indicator of healthy adults of the same age and sex, that is, below two standard deviations of the average of the named parameter. [14]

Causes of cancer cachexia

A decrease in the total nutrient intake for cancer patients.

a. Most cancers is accompanied by anorexia. Often the loss of appetite is one of the main symptoms, suggest the presence of a tumor. Also lead to anorexia and some physiological disorders, such as a change of taste in cancer patients.

b. To reduce the consumption of nutrients and cause specific metabolic processes specific to cancer. Identified a number of substances produced in the body when cancer process and lead to a decrease in nutrient intake. In this matter, for example, is cachectin - produced by the tumor. Cachectin affects the hypothalamus lamicheskie centers, contributing to the development of anorexia and cachexia.

a. Many tumors of digestive tract and mouth causing diarrhea disorders, such as nausea, vomiting, dysphagia. The result is a significant reduction in nutrient intake.

In some cases, the cancer patients develop depression, leading to a decrease in food consumption.

B. Metabolic. In patients with cancer processes observed numerous changes in the protein, fat and carbohydrate metabolism.

For cancer cachexia inherent negative protein and energy balance, resulting from eating disorders, and metabolic disorders. [15]

Currently, anorexia-cachexia syndrome is seen as the result of interaction between the tumor and the body, but the nature of it is not well understood [17,18]. It is known that due to the specific effects of the tumor increases the secretion of pro-inflammatory cytokines that initiate the development of a systemic inflammatory response [19], which is characterized by persistent and increased production of tumor necrosis factor - α (TNF-α), interleukin-1β (IL-1β), interleukin 6 (IL-6) and interferon-γ (IFN-γ) and the induction of acute-phase response. Of course, if you have an infectious lesion is useful because it allows you to activate the immune system and speed up recovery. However, in patients with cancer paraneoplastic processes lead to the development of a state of chronic inflammation, reinforcing cachexia and immunosuppression. [24] As shown in the experiments, the appointment of cytokines (TNF-α, IL-1β, IL-6 and IFN-γ) leads to symptoms of anorexia and malnutrition [19-23]. It should be noted that for the anorexia-cachexia syndrome is characterized by a decrease of skeletal muscle mass with relative preservation of visceral protein. [25] These global changes are a reflection of the complex metabolic process of rebuilding and in skeletal muscle, and liver of each patient. With the rate of protein synthesis in skeletal muscle slows down [26], while the breakdown of protein increases or remains the same, and in the liver accelerates the synthesis of acute phase proteins (Fig. 1) [27].
Pic. 1. The pathogenesis of the syndrome of anorexia - cachexia. [26]

Metabolic protein can develop by the non receipt of the protein needs of the body. When insufficient intake of protein has place there is always developing of protein deficiency. Excessive intake of protein in the body as a result of overeating or unbalanced diet (food high in protein), also leads to disturbances in protein metabolism. Another reason for the breach of protein metabolism may be to change the amino acid composition of the protein consumed. In various pathological conditions of the stomach and intestines (congenital, chronic disease of which are accompanied by malabsorption) can break the breakdown of proteins and amino acid absorption in the gastrointestinal tract.

Violation of the protein content in blood plasma can be the type—giperproteinemia (increased protein) or hypoproteinemia (decrease).

Hypoproteinemia can be either inherited or acquired as a result of liver failure, protein deficiency, burns, significant blood loss, and kidney disease.

Semiotics VIOLATIONS protein metabolism

Types of protein deficit

1. Kwashiorkor - unbalanced nutritional deficiency of the protein.
2. Malnutrition - a balanced, nutritional deficiency.

Symptoms of kwashiorkor:
• low body weight;
• pronounced edema, ascites, often;
• apathy, lethargy, low physical activity;
• delayed mental and physical development;
• low blood levels of proteins (especially albumin), lipoprotein, potassium, magnesium, and phosphate;
• immunodeficiency.

Disease with a poor prognosis and high mortality.

Symptoms of malnutrition:

• low body weight;
• swelling;
• delay in mental and physical development are not typical;
• The content of the protein at the lower limit of normal, reduced levels of lipoproteins, glucose;
• high levels of ketone bodies, ketoacidosis;
• immunodeficiency.
Forecast malnutrition more favorable.

Common symptoms of an incorrect, unbalanced diet with a deficiency of essential amino acids:

• Violation of the growth and development of children;
• low body weight;
• loss of appetite, poor digestion of protein foods.

With a deficit of a particular amino develop specific manifestations of its failure. Lack of phenylalanine causes a decrease in thyroid function (hypothyroidism). Manifested in the absence of tryptophan deficiency anemia, pellagra, blurred corneal, cataract. Methionine deficiency leads to obesity, gipokortitsizm, disruption of cholesterol exchange.

In violation of protein digestion and absorption of amino acids says:
• weight loss;
• intoxication due to impaired digestion of proteins with the release of toxic substances (indole, skatole, phenol, etc.);
• lack of proteolysis of muscle fibers, etc.

Thus, the expression of protein metabolism disorders have severe clinical outcomes and well understood. In this regard, we have developed a method for diagnosis of latent (hidden) forms of violation of protein metabolism, with use of the drug DINO96 as pharmacological test that can form the basis of tests to detect early forms of the above abnormalities occurring in violation of protein metabolism.
Description of the method

Quantitative values for total plasma protein were determined by the standard method for non-invasive blood analyzer AMP ("BIOPROMIN", Ukraine).

The principle of operation of the analyzer AMP is based on processing behavior of temperature indicators in five biologically active points: bifurcation of the carotid artery (left - Shh and TSD - right) in the axillary (T and T aksd akss) and abdominal (Tabd) areas up to 0, 000°C.

Studying the relationship of temperature changes in the reference points and the cellular, biochemical and other processes in the organism and its main kompartamentah allowed by a program "Success", to develop a methodology for determining the 128 blood parameters characterizing the basic parameters of homeostasis of the body, including the total protein of blood plasma. [28-33] Values of total plasma protein was determined by the standard method for noninvasive analyzer AMP ("BIOPROMIN", Ukraine) in mmol / L before and after 30, 60, 90 minutes, if necessary after 120 minutes minutes after a single application of 0.2% solution Dino 96 (applying to the skin of the anterior surface of the body of the drug).

Research results and discussion

Noninvasive (ILA) diagnostics performed 65 patients before and after pharmacological (DINO96) test (30, 60, 90 minutes, and if necessary, check the level of total plasma protein was carried out at 120 and 150 min). Of these, 10 persons (15.3%) to the use of pharmacological (DINO96) test revealed metabolic protein. Of them to the test in 2 (3%) patients showed a reduction in the total protein in the blood plasma of 53.73, 59.11 - at the rate of 60 - 85 mmol / l (Table 1).

Table1.

<table>
<thead>
<tr>
<th>time of registration</th>
<th>Pretest / mmol / l</th>
<th>30 min/ mmol/l</th>
<th>60 min/ mmol/l</th>
<th>90 min/ mmol/l</th>
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<tr>
<td>53.73</td>
<td>57.09</td>
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<tr>
<td>59.11</td>
<td>65.00</td>
<td>73.75</td>
<td>74.47</td>
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</table>

In this case, since the pharmacological (DINO96) test in 1 patient, there was normalization of the 30 minutes, the other for 60.

In 6 (9.3%) patients with normal total plasma protein after pharmacological (DINO96) test showed a reduction in the level of total protein, which ranged between 51.89 - 59.92 mg / dL. Restoration of the total protein concentration to normal levels occurred in 6 people (Table 2, 3).
Table 2.

<table>
<thead>
<tr>
<th>time of registration</th>
<th>Pretest / mmol/l</th>
<th>30 min/ mmol/l</th>
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<td></td>
<td></td>
<td>55,96</td>
<td>75,42</td>
<td>76,19</td>
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<tr>
<td></td>
<td>75,11</td>
<td>55,96</td>
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<td>76,19</td>
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<tr>
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<td>69,74</td>
<td>69,59</td>
<td>58,64</td>
<td>73,26</td>
</tr>
</tbody>
</table>

It should be noted that the appearance of hypoproteinemia was found for 30 minutes in 3 patients, in 60 minutes - in 2 and 1 in 120 minutes.

Table 3.

<table>
<thead>
<tr>
<th>time of registration</th>
<th>Pretest / mmol/l</th>
<th>30 min/ mmol/l</th>
<th>60 min/ mmol/l</th>
<th>90 min/ mmol/l</th>
<th>120 min/ mmol/l</th>
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<td>75,42</td>
<td>75,85</td>
<td>51,89</td>
<td>76,02</td>
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</table>

Thus, the latent (hidden) hypoproteinemia was found in 9.3% of the investigated patients. The decrease in total plasma protein after pharmacological (DINO96) test and its restoration to normal values attributed to the increased need for total protein in metabolic processes, its increased consumption. This process occurs hypoproteinemia consumption.

Two patients after pharmacological (DINO96) test at 30 and 60 minutes. found increase in total plasma protein - 88.56 and 109.41 mg / dL.

The reduction to the level of normal values occurred at 30 and 60 minutes
Table 4.

<table>
<thead>
<tr>
<th>time of registration</th>
<th>Pretest / mmol/l</th>
<th>30 min/ mmol/l</th>
<th>60 min/ mmol/l</th>
<th>90 min/ mmol/l</th>
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<td></td>
<td>77,23</td>
<td><strong>109,41</strong></td>
<td>61,62</td>
<td>78,26</td>
</tr>
</tbody>
</table>

During the pharmacological test we found that with the hyper-proteinemia Dino96 drug lowers the concentration of total plasma protein. With use of the drug causes hypoproteinemia normal levels of total protein. Thus, the drug has proteinreguliruyuschim (baseband schim) action.

In this regard, it can be assumed that the drug Dino-96, in confirming the data obtained will take its place among the drugs correcting protein metabolism.

**CONCLUSIONS**

1. The effect of the drug on protein metabolism Dino96 is found. Designed pharmacological test to identify violations of protein metabolism is found.

2. Pharmacological Test (Dino96) reveals reduction of the concentration of protein in the blood plasma - hypoproteinemia consumption and latent gipoproteinemia.

3. It was revealed that the drug hypoproteinemia Dino96 increases the concentration of protein in the blood, at Hyperproteinemia - decreases, nomalizuya his performance.

4. The facts Dino96 effects of the drug on protein metabolism svidetelst-exist on the need for further research aimed to confirm the results in diseases that occur in violation of protein metabolism.

5. Given the good results once the drug DINO96, it is necessary to continue to study the therapeutic effects of coursework in various diseases associated with impaired protein metabolism

6. Non-invasive blood analyzer AMP pharmacological (Dino-96) test can be used to study protein metabolism and be recommended for dynamic observation of pharmacotherapy as Dino-96, and other drugs.
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Noninvasive (AMP) diagnostics to assess the impact of the drug on calcium metabolism DINO96

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2013

Annotation: There is the material on the effect of the drug on DINO96 calcium. There is also possibility of the normalization of calcium metabolism in various diseases using the drug DINO 96. Non-invasive method (AMP) diagnosis holding pharmacological test (Dino96) is recommended in order to detect latent forms of hypercalcemia, hypocalcemia, hypocalcemia consumption and the possibility of the normalization of calcium metabolism in hypo-and hypercalcemia.

The role of calcium in the human body is extremely high. It is a necessary component of many metabolic processes occurring in the body, the following are the most important ones:

1. Regulation of permeability and making stable cell membranes;
2. Maintenance of normal excitability of nerve tissue and contraction of muscle fibers;
3. Participation in the intercellular connections that provide adhesion of cells at tkaneobrazovanii;
4. Activator of many enzymes and hormones, the most important components of hemostasis;
5. Participant in the immune response, has antiallergic;
6. Promotes the release of hormones and neurotransmitters and intracellular action of several hormones.
7. Is involved in the reduction of cholesterol and fibrinogen in the blood;
8. Changes in pO² blood;
9. Exhibits antioxidant effects;
10. Performs plastic and structural functions, being a part of the main mineral component of bone and tooth tissue (dentin) - oksiapatita, microcrystals that form a rigid structure of bone tissue;
11. Promotes excretion of salts of heavy metals and radionuclides.

The main food sources of calcium are milk and dairy products: yogurt, acidophilus milk, yogurt, cheese, cottage cheese. Content of up to 100-150 mg of calcium per 100 grams. However, in order to get the required 800 or so more than 1200 mg of calcium from these products, you need to drink 0,65-1,0 liter of milk or eat 650-800 grams of cottage cheese a day. Another rich source of calcium include beans, in which the content of this element also is 100-150 mg per 100 g of calcium-rich beets, turnips, peas, green onions, spinach, horseradish,
parsley, dandelion, yarrow, nettle, red clover and brown algae. However, after heat treatment, the calcium in these foods lose their properties (ionized form).

In the bloodstream calcium can be found in three forms: ionized associated with proteins and complex. Integrated fraction is about 10% of the total amount of calcium and a calcium compound phosphate, bicarbonate, citrate, and other ions. The fraction bound to proteins is approximately 40%, with the main binding protein is albumin. Ionized fraction is about 50% of total serum calcium. It is considered the physiologically active fraction, which is not only under the control of humeral mechanisms, but also the effect on the secretion of hormones. The decrease in serum concentration of ionized calcium is the main impetus for the formation and secretion of parathyroid hormone (PTH). The relative constancy of the calcium concentration in the blood serum is maintained by a feedback mechanism between the serum concentration of this ion and secretion of PTH. Calcium-sensing receptor parathyroid react quickly to changes in serum ionized calcium, causing increased formation and secretion of PTH.

Calcium absorption occurs mainly in the upper small intestine as a monobasic salt of phosphoric acid. Of the total amount of calcium present in the body, 98.9% are located in the bones, 0.51% - in the teeth, and 0.51% - in the soft tissues. The remaining 0.08% is in the blood plasma and extracellular fluid of soft tissues. Approximately half of this amount is related to serum proteins, mainly to albumin. The other half is calcium that can pass through the membrane. Sphingosine can mobilize Ca$^{2+}$ from intracellular stores and controls the specific Ca$^{2+}$ channel.

We know that all mammalian cells, except red blood cells, organelles, can accumulate Ca$^{2+}$ against an electrochemical gradient and energy-dependent manner.

Picture 1 shows the stages of the ATP hydrolysis of calcium ATPase and the associated transport of Ca$^{2+}$ across the membrane.

Pic.1. Calcium transport and ATP hydrolysis (ATP)
L-glutamate is the main mediator of the excitation in the synapses of the nervous system of vertebrates. Identified numerous glutamate receptors, which are separate from the rapid conduction of excitation is also a critical factor in the plasticity of synapses. On the kind of amino acid - arginine and glutamine, is in a critical situation in the field of transmembrane receptor dependent permeability ratio of Ca\(^{2+}\) / monovalent cations: glutamine provides high and arginine - almost zero permeability to Ca\(^{2+}\). Violations of Ca\(^{2+}\) -channel permeability data lead to a number of neurodegenerative diseases, including Parkinson's disease, stroke and epilepsy. [2]

At the heart of the formation of focal necrosis in the background of cerebral ischemia are fast reactions glutamate-calcium cascade developing in the first, minutes and hours after the vascular incident and is the main content of the period of "therapeutic window." [3-6]

In the development of glutamate-calcium cascade are three main phases: induction (start), amplification (gain damaging potential) and expression (final stage of the reaction, directly leading to the death of the cell) (Pic. 1).

Decreasing the amount of ATP in the ischemic zone and compensatory activation of anaerobic glycolysis in response to hypoxia caused an increase in inorganic phosphate, increased lactate production and cations H\(^{+}\), which causes the formation of metabolic acidosis. In addition, the splitting of the neuronal ATP leads to a "blackout" Na\(^{+}\) / K\(^{+}\)-ATPaznoy enzyme system that controls energy-dependent ion transport. [7]

Violation of active ion transport causes passive outflow of K\(^{+}\) from the cells, the influx of Ca\(^{2+}\), which leads to depolarization of the cell membranes. H\(^{+}\) cations continue to accumulate intracellular.

Along with the primary passive influx of Ca\(^{2+}\) into the cell through voltage-gated (voltage-controlled) Ca\(^{2+}\) channels violated sequestration of calcium in the mitochondria and endoplasmic reticulum due to lack of oxygen and ATP. [8-9] In addition, since the cations H\(^{+}\) and Ca\(^{2+}\) compete for the same binding site, the accumulation of acid valences within the cell can cause the release of large amounts of Ca\(^{2+}\) from the organelles. [10-11] The accumulation of intracellular Ca\(^{2+}\). in cerebral ischemia creates an overload of mitochondria with uncoupling of oxidative phosphorylation and increased catabolic processes. [12-14] This is accompanied by a transition of Ca\(^{2+}\) into the active form through binding to an intracellular receptor, calmodulin, which leads to activation of calmodulin dependent protein, lipases and endonucleases, DNA fragmentation, cell death. [15-16]
Thus, even at the early stages of the cascade pathobiochemical running deficits macroerags, the process of accumulation of intracellular calcium, which is one of the key mechanisms of the destructive processes underlying the necrotic death of neurons. [17-22]

It should be noted that the excessive accumulation of intracellular Ca2+ and the transition to the active form of calcium through binding to an intracellular receptor calmodulin cause activation of calmodulin-dependent intracellular enzymes, phospholipases, protein kinases, endonucleases. "Run" cascade of enzymatic reactions resulting in multiple injuries biomacromolecules and ultimately cell death. [5,23,24]
Particularly destructive decay of phospholipids in the outer cell membrane and in the membranes of intracellular organelles. Within a few minutes of ischemia, the release notes of the membranes and dokozeugazhkovoy palmitic acid, which indicates the destruction of phosphatidyl choline and phosphatidyl ethanolamine. It is shown that with 30 minutes of ischemia destroyed about 16% of membrane phosphatidylethanolamine and released about 37% of free arachidonic acid. [25-27]

Agonist induced increase in the concentration of calcium in the cytoplasm is the result of its receipt from the outside and from the intracellular stores of calcium. A convenient model for the study of calcium metabolism are human platelets. They are easy to select, they are easily loaded with calcium fluorentechnymi probes on the surface of many different hormone receptors. Inducers of platelet aggregation exercise their action by increasing the concentration of cytoplasmic calcium. [28] Platelets are well studied in the exchange of second messengers. Growth kinetics of cytoplasmic calcium concentration and its entry into the cell is described in detail in the book. [29]

In calcium-free medium kinetics of calcium release into the cytoplasm is similar to that in an environment with calcium, but the duration of the calcium response is reduced by several times. [30] This suggests that the duration of response required calcium influx from the outside. Manganese is blocking the entry of calcium into cells.

Possible ways Ca entry into the cell, depended on receptor is not related to activation of ion channels: through the carrier by Na / Ca-exchange and endocytosis.

The idea of the existence of a calcium carrier lipid was launched after the discovery of the phosphoinositide cycle. Phosphatidic acid was considered as a candidate for such role. [31-33] This compound accumulates in the cells in the first few seconds after exposure to agonists that activate fosfoinozidny exchange. [34] Ionophore action of phosphatidic acid has been demonstrated in extracellular oscillating systems. [31,33,35]

Exchange of ionized calcium in the body is made up of several different directional flows:

1. absorption in the small intestine and entering the bloodstream;
2. bloodstream and deposits in the skeleton (mineralization);
3. release, mobilization of bone into the blood stream;
4. admission to the soft tissue (nerve, muscle, etc.) and out of the bloodstream;
5. secretion from the blood into the lumen of the intestine and remove their excreta (primary route of elimination of calcium from the body);
6. secretion of urine and back reabsorption in the renal tubules (the urine is released not more than 20-30% of the calcium that is output from the body).
In this case, the calcium metabolism is under strict regulatory control of complex, multi-level system of hormone (PTH parathyroid hormone, 1,25-dihydroxy-cholecalciferol (1,25 DGHK) calcitonin CT and its predecessor katakaltsin), which is an essential component of calcitriol (vitamin D).

The physiological role of calcitonin in humans is not well and needs further clarification. However, there is an assumption that calcitonin is involved in maintaining a steady state of calcium balance. According to this theory, calcitonin has a role in the transport of calcium after intestinal absorption in liquid space of bones, where it is temporarily stored and from which can be removed if necessary to the interstitial space in between the ingestion of calcium.

Installed a number of hormone involved in calcium metabolism and maintenance of the integrity of the skeleton, which, however, has only a supporting role: the growth hormone, prolactin, sex steroid hormones, thyroxine, and cortisol. However major hormones regulate the calcium homeostasis by influencing the level of calcium deposits in the bones and his removal from them, and the renal excretion of calcium absorption in the gastrointestinal tract.

The physiological effect of PTH target tissue covers kidney, bone, and gastrointestinal tract. In target tissues PTH acts on specific receptors in the cell membrane that are linked to adenylate cyclase, resulting in the release is cAMP, which transmits impulses within the cell. The impact of PTH on the kidney is accompanied by increased urinary excretion of cAMP, which is important differential diagnostic value. Physiological effects of PTH in the kidney is the regulation of release of calcium, phosphorus and other ions, as well as the impact on the formation of 1,25-DGHK. In the absence of PTH, 97% of the filter schegosya calcium is reabsorbed in the kidney tubules. PTH increases tubular reabsorption of calcium, raising the threshold of renal reabsorption of this ion and, therefore, serum concentrations of calcium. PTH decreases the renal reabsorption of phosphorus, lowers the threshold for the reabsorption of phosphorus and perpetuate the level of excretion of phosphorus at a low concentrations in the blood serum, so that the overall effect of PTH is aimed at reducing serum phosphorus. In addition, PTH affects the metabolism of cholecalciferol, it stimulates the kidneys 1.25 DGHK from its precursor 25-hydroxy-cholecalciferol (25-MCC). Studied the physiological effect of PTH on bone, which is what causes the increase in PTH level of resorption, in which suppressed collagen and mineral phase and is calcium release into the circulation.

Cholecalciferol is produced in the skin from 7-dehydrocholesterol by a photochemical reaction. The first stage of the transformation of cholecalciferol in the final biologically active form in the liver and is the hydroxylation at C-25 and the formation of 25-MCC. The latter undergoes further hydroxylation in the kidney at the C-1, resulting in a 1.25-DGHK - an important biologically active metabolite and hormonal form of cholecalciferol. The kidneys are a place of education is one digidroksimetabolita - 24,25 dihydroxycholecalciferol (24,25 DGHK), suggesting that it also plays a role in the metabolism of calcium and phosphorus, but this role, as well as the role of other di-and trigidroksimetabolitov, finally installed. Gipokaltsiemii renal synthesis is aimed at the 25-hydroxylation of MCC at C-1 and 1.25-DGHK
education, and when the normal serum calcium is a transition to the formation of 24,25 DGHK. The first system consists of calcium, phosphorus, PTH, and by 1.25 DGHK: This system regulates the formation of 1,25-DGHK intended to meet short-term needs for calcium and phosphorus, and works on the principle of feedback. The second system, which seems to be designed for the regulation of long-term needs, represented a growth hormone, prolactin and sex steroid hormones, but is still not determined which of these hormones play a major role in certain phases of this regulation. The main impact of biological objects is 1.25 DGHK bone and gastrointestinal tract, where it binds to specific receptors of the cell nuclei. Despite the fact that calcium is able to passively diffuse through the wall of the intestine in sufficient supply it with food, the active transport of calcium through the intestinal wall without 1.25 DGHK virtually absent, 1.25-DGHK leads to a significant increase in the active transport of calcium and causes an increase in its serum concentrations. After treatment with 1.25 DGHK nekalsifitsirovanny osteoid, which is observed in rickets and osteomalacia, undergoes remineralization. The mineralization process may affect the extracellular concentration of calcium and phosphorus, as well as the factors that regulate the negotiation process of resorption and bone mineralization. Increased bone resorption was observed after an overdose of vitamin D or its biologically active derivatives. In addition, 1,25-DGHK have a biological effect on the parathyroid glands, kidneys and muscles. In cells paraschito-prominent glands have specific receptors sensitive to vitamin D, and in animal experiments proved that its derivatives can alter the level of PTH secretion. Treating patients with hypoparathyroidism 1.25 DGHK the phosphorus reabsorption in the renal tubules, followed by a change in its serum concentrations can be increased. Hypotonia, which is the most common symptom of vitamin D, is a regimen of 1.25 DGHK. [75]

The test system is the primary target of CT bone, where the hormone inhibits the resorption of the matrix, thus reducing the release of calcium and phosphate. This effect is independent of CT PTH. CT increases cAMP content in bone, affecting, apparently, to those cells that are not targets of PTH. CT also has a significant effect on the metabolism of phosphate. It contributes to the input of phosphate in bone cells, and periosteal fluid, reducing the yield of the calcium from the bones into the blood plasma. This entry can be accompanied by phosphate and calcium entry, judging by the fact that the effect of CT gipokaltsiemichesky depends on phosphate. Such action CT along with its ability to inhibit osteoclast-mediated bone resorption can explain the efficacy of this hormone in the fight with hypercalcemia in cancer. Precursor of human calcitonin is katakaltsin - peptide representing the C-terminal part. It also reduces the level of Ca\(^{2+}\) in the blood. [31,33,35]

Along with this, a necessary condition for full assimilation and use of calcium is the optimal provision of the body of ascorbic acid and other vitamins, including B2 and B6. Calcium absorption depends on the content in the diet of fat, protein, magnesium, and phosphorus. The ratio of calcium: magnesium = 1:0.5; calcium: phosphorus = 1:1.5. With an excess of fat is competition for bile acids, and much of the calcium output from the large intestine.

Alonso et al. [69] have shown that arachidonic acid at concentrations of 10-5-10-4 M also can carry a cell ions Ca, Mn, Mg, Ba and Co. Arachidonic acid transport of divalent cations from
the external medium into the cell was observed in experiments with platelets, neutrophils, thymocytes, cells in vitro. Given that in many cases, agonists stimulate phospholipase A \(^2\) +, splits arachidonic acid, a priori we can not exclude the role of this compound as a physiological Ca-ionophore. Theoretically, in ionophore transport across the plasma membrane Ca \(^2\) + ions are exchanged for hydrogen or any other counterion. Therefore, transport must be electrically neutral and Ca\(^2\)+ entry by this mechanism will not be accompanied by a change in membrane potential.

Transport of calcium in the body is carried out more than 100 proteins, calcium transport ATPase (ATPase), a constitutively expressed NO-synthase, and others.

Ca\(^2\)+ binding to many proteins have in their structure universal specific places. The most common is the EF-hand motiv1 and C2 domain.

EF-hand motifs are found in pairs, where the unit motif binds one Ca\(^2\)+. However, the dissociation constant of Ca\(^2\)+ vary depending on the protein itself (10-7 and 10-5M for the EF-hand), and (10-6-10-3M) for a C2 domain. About 100 known proteins have C2 domain. C2 domain and EF-hand not only the binding site of Ca\(^2\)+. For example, annexin - fosfolipidsvyazyvayuschy protein on the inner surface of the plasma membrane and is associated with the cytoskeleton. Ca\(^2\)+ channels and Ca\(^2\)+ ATPase also have Ca\(^2\)+ binding sites other than the C2 and EF-hand. Calmodulin (CM) was found in almost all cells of animals and plants. A typical animal cell contains more than 107 molecules KM, or almost 1% of the total cellular protein. CM functions as a versatile intracellular receptor for Ca\(^2\)+ involved in most of the processes governed by these ions. Interacting with the CM, Ca\(^2\)+ can alter the activity of approximately 100 enzymes. [1] The isoform of troponin C is CM. It is present in striated muscle, where regulates interactions between actin and myosin. CM like he has two pairs of Ca\(^2\)+ -binding EF-hands, localized at opposite ends of the peptide chain. The affinity of these sites for Ca\(^2\)+ is in the range 10-5 and 10-7M. Muscle cells are specialized, like smooth endoplasm-matic reticulum (ER), an organelle called the sarcoplasmic reticulum (SR), which captures from the cytosolic Ca\(^2\)+.

![Graph showing calcium levels in plasma and their effects on health parameters.](image-url)
Belkovy domain EF-hand (EF-hand motif) typical EF-hand consists of 12-membered loop bounded on two sides of a-helices, consisting of 12-14 amino acid residues. Six amino acid residues (positions 1, 3, 5, 7, 9 and 12 in the 12-membered loop) directly involved in the coordination of Ca$^{2+}$, and the ligands act as the oxygen atoms belonging to the carboxyl or hydroxyl groups of amino acids, peptide carbonyl oxygen atoms communication and the oxygen atoms of the water molecules held in Ca-binding loop. Conserved residue Glu, located at 12 loops can act as bidentantnogo ligand doniruya both oxygen atoms of the carboxyl group to bind the metal cation. Seven oxygen atoms involved in the binding of Ca$^{2+}$; are located at the vertices of the pentagonal bi pyramid, and the polypeptide chain as a twist around the metal cation [40, 41]. The primary structure of the Ca-binding loops largely determines the parameters of the binding of Ca$^{2+}$. That is why the primary structures of various calcium-binding sites characterized by a highly conserved [42]. However, the specificity and strength of binding of the metal cation is determined not only the primary structure of the loop, but also depend on the primary structure of this loop flanking helices [43] and spirals, which are located near the Ca-binding loop [44], as well as the interaction of the Ca-svyazyvayushih loops with each other. [45]

The main membrane protein sarcoplasmic reticulum - Ca$^{2+}$-ATP-ase, pumped into calcium ions. The rapid contraction and relaxation of myofibrils in each cycle of muscle contraction is mediated by the release of calcium from the sarcoplasmic reticulum and then re-capture it from the cytosol.

![Localization and troponin tropomiozin](image)

Protein kalsekvestrin (2 kDa) and other Ca$^{2+}$-binding protein with high affinity for Ca$^{2+}$ (55 kDa) are located in the interior of Wed For this protein are characterized by large number of calcium-binding sites (more than 40) with a low affinity (Kdiss submillimolyarnom is in range). [39] Because of this protein in the sarcoplasmic reticulum terminal tanks may accumulate large amounts of calcium without the formation of an insoluble precipitate. It is believed that within the terminal tanks kalsekvestrin Wed connects most of Ca$^{2+}$ flowing into them at work Ca$^{2+}$-ATPase. Kalsekvestrin not only serves as a buffer for Ca$^{2+}$ within the terminal tanks, but also concentrates the Ca$^{2+}$ near Ca$^{2+}$ channels, thereby increasing the rate of release of Ca$^{2+}$.

A similar buffer role in non-muscle cells plays ER Ca$^{2+}$ - binding protein - or kalregulin kalretikulin.

It is now known that the phosphatase RR2V widespread and is present in many tissues. It was initially identified as Ca$^{2+}$ - binding protein of the nervous tissue, which has been called calcineurin. Only later it was found that it has a phosphatase activity, and that it is a regulatory subunit of Ca$^{2+}$ - binding protein calmodulin. Unlike other members of the superfamily Ca$^{2+}$ - binding protein calmodulin in response to the calcium signal can bind to many different target proteins and regulate their activity. [46] This phosphatase is composed of three subunits: calcineurin A (catalytic subunit), calcineurin B (calmodulin-like regulatory subunit) and
calmodulin directly. B-subunit determines the substrate specificity. Calcineurin can be activated either by increasing the concentration of Ca\(^{2+}\) in the cytosol, or as a result of phosphorylation of calcineurin B, the latter so increases the affinity for Ca\(^{2+}\), activation can occur when the concentration of Ca\(^{2+}\), characteristic of the state of rest.

Another family of Ca\(^{2+}\)-binding proteins - a constitutively expressed NO-synthase. In 1987, the endothelium relaxation factor (EDRF) was identified with NO [47,48], the synthesis of which is constitutively in endothelial NO-synthase expressible.

Constitutive NO-synthase (NOS) - the calcium-calmodulin-dependent enzymes. They are divided into neuronal (nNOS - I type) and endothelial (ecNOS - III type) isoforms, which are revealed in the endothelial cells, or neurons, platelets, neutrophils and other cells (Table 1). All three types of synthases as a cofactor used: methylenetetrahydrofolate dehydrogenase (NADPH), flavinadeninucleotid (FAD), flavin mononucleotide (FMN) and possibly tetrahydrobiopterin (similar in structure to a fragment of folic acid). [49,50] The presence of ecNOS characteristic only epithet cells of blood vessels. [51] The formation of endothelial nitric NO is an important component of the regulation of the tone of blood [52,53], and the tone of the lymphatic vessels [54], and to prevent blood clots.
Table 1. Tissues, organs and cells, which showed a constitutively expressed NO-synthase.

<table>
<thead>
<tr>
<th>Cells</th>
<th>Tissues and organs</th>
</tr>
</thead>
<tbody>
<tr>
<td>endothelial platelets</td>
<td>The vascular endothelium</td>
</tr>
<tr>
<td>endocardial cells</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>cardiomyocytes</td>
<td>The peripheral nervous system</td>
</tr>
<tr>
<td>Megakarioblasty</td>
<td>adrenals</td>
</tr>
<tr>
<td>Monocyte / macrophage line J774.2</td>
<td>retina</td>
</tr>
<tr>
<td>neuroblastoma cells</td>
<td>skeletal muscle</td>
</tr>
<tr>
<td>Pituitary GH3 cells lines</td>
<td></td>
</tr>
<tr>
<td>kidney epithelial cells</td>
<td></td>
</tr>
<tr>
<td>mast cells</td>
<td></td>
</tr>
<tr>
<td>mesangial cells</td>
<td></td>
</tr>
<tr>
<td>Non-adrenergic non-cholinergic neurons</td>
<td></td>
</tr>
</tbody>
</table>

At the same time, NO-padikaly stimulate neutrophil chemotaxis [58], and in the culture of human endothelial cells induced by TNF intensified synthesis of interleukin-8. Such regulatory physiological effect of NO appears at nanomolar concentrations, significantly lower than the "cytotoxic" concentrations observed upon activation of monocytes and macrophages. NO synthesis in endothelial cells is induced by a number of physiological stimulants and vasoactive compounds (Table 2) [59], including ionophore Ca$^{2+}$ A23187.

Table 2. Stimulators of NO synthesis in endothelial cells

<table>
<thead>
<tr>
<th>physiological stimulants</th>
<th>Vazoaktiv connections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in blood flow velocity, shear stress stress</td>
<td>acetylcholine</td>
</tr>
<tr>
<td></td>
<td>ADP, ATP</td>
</tr>
<tr>
<td></td>
<td>bradykinin</td>
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<td>Protein gene kalitsitonina</td>
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<td>ionophore Ca2+A23187</td>
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<td>cholecystokinin</td>
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<td>Vasoactive intestinal peptide</td>
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<td>leukotrienes</td>
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<th>Change in blood pO2</th>
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Neuronal NO-synthase is a soluble homodimer with a molecular mass of about 150 kDa. It consists of 1 mol of FAD, FMN, tetrahydrobiopterin, each molecule contains a calmodulin-binding center that Ca2+ dependent regulation of the synthesis of NO and the iron atom that is part of the heme prosthetic group. [60] demonstrated its significant homology Cytochrome-P450 reductase [61,62] and the presence of NADPH-activity [63,64].

NADPH-activity can be used as a marker for the constitutive NO-synthase [50], but also revealed the presence of false-positive results [65]. The maximum activity of the enzyme (oxidation of L-arginine > 300 nmol / mg per min) was observed at concentrations of Ca2+ -0.4 mM.

It should be noted that the study of neurons containing NO-synthase, began more than 40 years ago, when histochemically in the brain were found cells with high activity of NADPH-diaphorase. Morphologically diaphorase activity (determined by Nitroblue tetrazoniya in diformazan) in cells is an indication of the presence of NO-synthase. [50] However, the possible false positive results-. [66] The highest enzyme activity was detected in neurons of the cerebellum and in astroglia. Lower level of activity observed in the hypothalamus, midbrain, striatum, cortex, hippocampus and medulla oblongata [66,67].

Neuronal and endothelial NOS inactive at normal levels of Ca2+ in the cell and start to synthesize NO in response to increased calcium concentration in the cytosol, causing the binding to CaM these constitutive enzymes. Prolonged elevation of calcium leads to constant product NO. In contrast, production of inducible form of NOS does not depend on the level of intracellular calcium in the normal level it is limited only by the amount of enzyme and substrate and the presence of cofactors [77].

One of the mechanisms of regulation of products NO is phosphorylation of molecules of NO-synthase. Constitutive phosphorylation of cAMP-NOS zavismosti protein kinase, protein kinase C, cGMP-dependent protein kinase, Ca2+ - kalmulinzavisimoy protein kinase leads to a reduction in the activity of these enzymes. On the other hand, the protein phosphatase calcineurin can be dephosphorylate-NOS, causing increasing its catalytic activity [77].

Installed calcium - oxalic acid (found in chocolate, spinach). High fat, phytic acid (found in grains) - inhibit the absorption of calcium.

Insufficient intake of calcium in the body, and even a slight decrease in its level in the blood leads to increased release parathyroid hormone (Paraty-stimulating hormone).

This increases the excretion of calcium from the bones into the blood, causing bone demineralization, bone loss (osteoporosis), bleeding capillaries, and reduced total body resistance to diseases.

Shown that calcium supplementation significantly (by 25%) reduced the incidence of colorectal cancer in men and women of the middle aged and elderly. This effect is due to the ability to bind calcium secreted by the liver into the intestinal lumen, bile acids that can irritate the wall of the rectum. On the other hand, an excessive increase in calcium levels
(hypercalcemia) has a deleterious effect on many enzyme systems and cellular functions, causes cardiac abnormalities, calcification (извествление), kidney, heart, aorta, coronary arteries with an irreversible disorder of their functions. [75]

Lack of calcium in the diet increases the risk of rickets in children, osteoporosis in adults, violates the development of the skeleton and teeth, increases the risk of cardiovascular disease and some cancers, especially colon cancer.

Insufficient calcium can be intake during childhood and adolescence hampers optimal genetically predetermined peak bone mass and density, significantly increasing the risk and severity of the subsequent development of osteoporosis.

Reduction of ionized calcium in adults leads to violations of bone mineralization, reduction and loss of muscle tone, increased excitability of the motor neurons and seizures.

Presented an overview of the huge role of calcium can be seen in ensuring vitality. Change in its concentration in various kompartaments leads to various pathological disorders: from changes in blood clotting, nerve excitability, immunity, and others, up to ischemia (cell death).

Popular calcium supplements, such as lactate, gluconate and others apply for a lack of calcium in the body. However, their use is not always a positive effect on the body. For example, one of the most influential medical journals in the world, "BMJ» (British Medical Journal) published a major study on the subject. A team of scientists from New Zealand, the UK and the U.S. have reviewed 11 major studies on the prevention of osteoporosis with calcium supplements.

This type of research in medical science is called a meta-analysis, and today it is very popular. With skillful use it to pull the old works of something new and unexpected. It happened at this time, when scientists have summarized observations of nearly 12 thousand people, conducted earlier in the 11 different studies. There is a very sad outcome: drugs with calcium increase the risk of heart attacks by 31%. Why have not noticed this before? In six of the 11 older works that are included in this meta-analysis, such a "heart attack" trend was observed, but was not statistically significant. When all studies were combined, the trend to an absolutely true fact: 31% - this is very important. Conclusion of scientists is clear: the use of calcium supplements to prevent osteoporosis should be reconsidered. And their colleagues go even further: they argue that osteoporosis should not be used not only to drugs with a calcium, but also complex products that contain more and vitamin D. [70]

It is now established that, to avoid artifacts should focus venipuncture technique during blood sampling [76] to investigate the content of calcium. Blood samples for research to produce better on an empty stomach. However, during the day as usual after taking food, and foods containing large amounts of calcium, serum calcium oscillations are 0,13-0,20 mmol / l and fasting before collecting blood is optional. The comparative evaluation of the dynamics of calcium concentration in any patient greater value at the same time to determine the concentration of total protein and especially the albumin fraction, since fluctuations in the
concentration of serum total calcium may be a reflection of impaired concentration of total protein and albumin.

There are controversies regarding the diagnostic value of routine measurement of the concentration of ionized calcium in patients with hyper-kaltsiemiey. According to the observations [75], the majority of patients the ratio levels of ionized calcium and total calcium levels - is constant. It is therefore considered that the determination of ionized calcium have diagnostic value in patients with hypercalcemia, accompanied by significant violations of the concentration of albumin in tumors of different localization, multiple myeloma.

Clearly, the role of calcium in the activity of cells and tissues of the body is extremely complex and research in this area has been going on for a long time. Calcium is an important place of macro- and micronutrients, as involved in a large number of metabolic processes in the organism. Developing reliable screening method determining the state of calcium, as well as searching for drugs that can directly and indirectly to recover calcium metabolism seems relevant. Us studied the calcium in patients with nosological syntropo and influence of the drug Dino-96's ability to restore normal levels of calcium in the blood in these patients.

Drug Dino-96 is a natural, mineral-amino acid composition with the richest natural substances. The product meets the needs of the body tissues, as it contains most of the well-known L-amino acids, micro and macro elements, including calcium.

Amino acids (protein components) contained in the substrate, it is on the other components in the proportions are found only in nature. Conserve natural stereochemistry, no synthetic amino acids. Thanks to the development of the internal molecular structure of the individual components of the substrate are represented as trace elements and are capable of direct penetration into the cells of the body, bypassing the typical way: the gastrointestinal tract - liver - circulatory system - the cell (of course, in the reduction).

The purpose of this study was to examine the state of calcium in 63 patients who received a consent form.

**Description of the method**

Quantitative indicators of calcium was determined by the standard method for non-invasive blood analyzer AMP ("BIOPROMIN", Ukraine)

The principle of operation of the analyzer AMP is based on processing behavior of temperature indicators in five biologically active points: bifurcation of the carotid artery (left - Shh and TSD - right) in the axillary (T and T aksd akss) and abdominal (Tabd) areas up to 0, 000S.

Studying the relationship of temperature changes in the reference points and the cellular, biochemical and other processes in the organism and its main kompartamentah allowed by a program "Success", to develop a methodology for determining the 128 blood parameters characterizing the basic parameters of homeostasis, including electrolytes (calcium, including). [71-74]
Indicators of calcium in the blood plasma was determined by the standard method for noninvasive analyzer AMP ("BIOPROMIN", Ukraine) in mmol / L before and after 30, 60, 90 minutes, if necessary after 120 minutes minutes after a single application of 0.2% solution Dino 96 application to the skin of the anterior surface of the body of the drug.

The reliability of the data is statistically valid.

Research results and discussion

Noninvasive (AMP) diagnostics performed in 63 patients before and after pharmacological (DINO96) test (30, 60, 90 minutes, and if necessary, check the level of calcium in the blood plasma was carried out in 120 minutes). Of these, 12 (19%) to the use of pharmacological (DINO96) test revealed hypocalcemia, which ranged from 1.63-2.24 mmol / L (N = 2.25 - 3.00).

Normalization of the test occurred 9 people after the pharmacological (DINO96). In this case, the restoration of the calcium concentration in the 30 minute study occurred in 6 people, after 60 minutes at the 2, and 1 patient - after 120 minutes.

In 9 (14%) patients with normal calcium levels after pharmacological (DINO96) test showed a reduction in the level of calcium, which ranged between 1.78 - 2.24 mmol / l. Restoration of calcium to normal levels occurred in 6 people, with a normalization of 3 people missing. One of them was the 90-minute study of calcium concentration in plasma reached a minimum value (up to - 2.54, in 30 -2.18 min, 60 min - 2.20, 90 min - 2.08). Thus, the latent (hidden) hypocalcemia was detected in 14% of the studied patients. The decrease in plasma calcium levels after pharmacological (DINO96) test and its restoration to normal levels associated with increased calcium needs in metabolic processes and consumption and an increase in consumption - hypocalcemia consumption.

In 6 (9.5%) evaluable patients showed an increased content of calcium in the blood plasma (giperkatsiemiya), which ranged between 3.17 - 4.27 mmol / l. At the same time two with normal calcium in the blood plasma giperkatsiyaemiya revealed after pharmacological (DINO96) test.

Thus, of the 63 patients studied the metabolism of calcium was detected in 27 (42.5%) patients, and hypocalcemia, as an explicit (12 people. is 19%) and latent (9 people. Is 14%) Predominated over hypercalcemia (9.5%). High levels of hypocalcemia (42.5%) associated with us the presence of chronic gastroduodenitis that interferes with the absorption of calcium in the intestine.

We found that hypercalcemia Dino96 drug lowers blood calcium. Gipokaltsiemiia use of the drug causes a normalization of calcium levels. Thus, the drug has a calcium-regulating (modulating) effects. Given the fact that the new, extended analysis of cardiovascular risks associated with taking calcium supplements, suggests that the previously reported 30% of the risk of myocardial infarction (MI) associated with taking calcium supplements, also extends to its combination with vitamin D. However, this strategy should be reconsidered because of the evidence of a 20% increased risk of MI and stroke in patients using this combination. The study
CONCLUSIONS

1. The influence of the drug Dino96 on calcium metabolism in the blood is found.

2. Pharmacological test with the drug Dino96 identifies as latency reduction, and an increase in the level of calcium in the blood, hypocalcaemia consumption and latent hypercalcemia.

3. Found that hypercalcemia drug Dino96 lowers blood calcium. Gipokaltsiemii use of the drug causes a normalization of calcium levels. Thus the Calcium effect of the drug is found in Dino96.

4. The facts on the effects of the drug Dino96 calcium metabolism dictate the need for further research aimed to confirm the clinical effects of pathological parathyroid glands, immune deficiency, the pathology of hemostasis and other diseases occurring in violation of calcium.

5. Given the good results once the drug Dino 96, it is necessary to continue to study the therapeutic effects of coursework in various diseases associated with impaired metabolism of calcium.

6. Non-invasive blood analyzer AMP can be used to study the metabolism of calcium (as Dino-96 pharmacological tests) and can be recommended for the dynamic observation of pharmacotherapy as Dino-96, and other drugs.
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Annotation: This article presents data on the influence of the drug DINO 96 for the content of glutamic acid in 51 patients with nosological syntropy. The possibility of normalizing the concentration of glutamate (glutamic acid, GLUTAMATE, GLU) in the blood using the drug DINO 96.

2012

Feature of chronic diseases in modern conditions is multifactorial pathogenesis and heterogeneity, due to violation of fundamental regulatory systems of the body. This leads to the weighting of the flow, this also involved the paired organs and other organs and systems in the process. The medical literature is widely used terms: syntropy, interference, multimorbid denoting the relationship of various diseases among themselves. Syntropy - Two or more pathogenetically related, naturally emerging diseases. At the same time the attention of researchers are increasingly attracted by the problem of multi-and comorbidity [1, 2, 3, 4, 5, 6, 7, 8]. While the growth of the multiple NOSTA disease with age reflects, above all, involutorial processes, the concept of comorbidity reflects a causal possibility of their combination, the latter being much less studied.

The problem of combining disease is difficult to preetsenimoe value [9, 10], being one of the most challenging faced by physicians [11]. Along with this nosological syntropy which is important for scientific and practical medicine [12], is particularly relevant in relation to commonly occurring and highly significant social pathologies of the nervous and cardiovascular system, gastrointestinal diseases, and musculoskeletal system.

WHO researchers have shown that the conduct of therapeutic and preventive measures are no longer able to change the looming situation and traditional approaches to the treatment of common diseases leading to huge economic losses and modest results (Ivashkin VT, IN Ulanova, 2006). The problem of low efficiency of therapeutic and preventive measures related to the absence of etiological orientation due to insufficient understanding of the key mechanisms of formation of the vast majority of multifactorial diseases (Weiss KM, Terwilliger JD, 2000).

Classes of diseases of the nervous, cardiovascular, digestive system and musculoskeletal system are the most resource-intensive, have a high degree of compatibility and plurality, you visit the hospitals and the duration of hospitalization, primary disability and premature mortality that takes justified their prevention and treatment at the level of one of the priority areas of medicine [13, 14].

Diagnosis in one patient, multiple disease is a characteristic feature of the present patient. The combination of disease increases with age from 1.8 the disease in one person (aged 15-29 years) to 2.4 (60 and older) women is slightly higher. Nosological syntropy observed in patients with insulin-dependent diabetes mellitus (IDDM), while they are more common chronic relapsing inflammatory processes in different locations. The multiplicity of related diseases - the most important feature of the modern
"cardiac" patients [15, 16, 17]. At the heart of syntropy or logical combinations of certain common diseases is their common risk factors and mechanisms of development [15]. Well-known combination of coronary heart disease (CHD) and diabetes mellitus, ischemic heart disease and hypertension, ischemic heart disease and erosive-ulcerous lesions of gastroduodenal zone [15, 17].

Along with this, combined pathology of the nervous, cardiovascular, gastrointestinal and musculoskeletal neglected. There are no data on the general pathogenetic mechanisms of lymphoma syntropy. Therefore, diagnosis and therapy of lymphoma syntropy currently remains clinically and socially significant problem. In this regard, search for pharmacological agents acting on the common pathogenetic mechanisms of development of lymphoma syntropy seems relevant.

The literature describes diseases and pathological conditions associated with changes in glutamate levels in the body: in particular, liver diseases, cardio-vascular system [9, 10], and delay physical and mental growth, nervous exhaustion, depression, epilepsy, somatogenic, intoxication and involutional psychosis neurotoxic states; polio, cerebral palsy, Down syndrome, muscular dystrophy, diabetes, hypoglycemic states, etc. In recent years, new data on the value of glutamic acid for the functioning of the central nervous system and its role in the development of diseases such as heart attacks, strokes and a variety of neuropathological conditions [11, 12].

When state is accompanied by a lack of glutamic acid compensatory mechanisms of the body can not prevent changes of hydrogen ion concentration, there comes a disturbance of acid-base balance. Reducing the concentration of glutamate decreases the glutathione content and weakens the body's resistance to hypoxia, both due to inactivation of enzymes pentozomonofosfatnogo cycle and by inhibiting tiofermentov tissue respiration. The reasons it may be: a decrease in minute volume of respiration, circulatory failure, pulmonary sarcoidosis, rheumatoid arthritis, acute pneumonia, etc. All of these pathological conditions are accompanied by a deficiency of glutamic acid.

Glutamic acid occupies an important place among the tissue metabolites, because of mutual transformation into each other all the essential amino acids must be converted at the beginning, glutamic or aspartic acid. The primary role in the redistribution of nitrogen belongs to glutamic acid, which is 25% of the total number of all (essential and nonessential) amino acids in the body. Therefore, these amino acids play an integrative role in nitrogen metabolism. However, this integrative role is not limited to just compensation for the shortfall in dietary amino acids. There is the phenomenon of "redistribution of nitrogen in the body." If there is insufficient protein in any one organ due to disease or hyperthyroidism (need a working hypertrophy) is a redistribution of nitrogen: protein "removed" from one of the internal organs and is sent to the other. The most common source of easily mobilized proteins are transport proteins of blood. When their stock is exhausted, the proteins used spleen, liver, kidneys and intestines. Proteins of the heart and brain are not being spent than ever, since this is the most important organs of the body. In this case, the redistribution of nitrogen in the body all the essential amino acids are transformed first into glutamic and aspartic acid, and then to those that are lacking in the working body. Although glutamic acid is considered a classic and essential amino acids, in recent years found that for certain human tissues glutamic acid is an indispensable and nothing else (no other amino acid) can not be vospolnima. In the body there is a kind of "foundation" of glutamic acid. Glutamic acid is consumed in the first place where it is needed most.

Glutamate is converted to glutamine, by adding ammonia molecule. Ammonia - a highly compound which is formed as a by-product of nitrogen metabolism and accounts for 80% of all nitrogenous toxins. By adding the ammonia, glutamic acid is converted into nontoxic glutamine, which is in turn included in the amino acid metabolism. This process - the only way to neutralize the ammonia in the brain. Given the detoxification effect of glutamic acid, glutamine, it is preferable.
Glutamic acid - one of the few compounds which, together with glucose can serve as a good source of energy supply to the brain. This is due to its ability to oxidize at a stage of formation mitochondrial α-ketoglutaric acid with the release of energy stored in the form of ATP. Biosynthesis of glutamic acid, carbohydrates, primarily glucose, is an extremely important mechanism for backup supply to the brain in the absence of glucose or carbohydrate food at very high physical activity. As an anion, glutamate is present in the proteins (myosin, casein, β-lactoglobulin, etc.), and a number of small molecules in the free form. In addition, glutamate is involved in the integration of nitrogen metabolism, biosynthesis of amino acids, carbohydrates, nucleic, n-aminobenzoic, folic (iteroilglutaminovaya) acids; i-AMP, p-GMP (which are intermediaries in the transmission of hormonal and neurotransmitter signals). Involved in the synthesis: enzymes that carry out redox reactions (NAD), serotonin (indirectly via tryptophan) is directly converted into γ-aminobutyric acid (GABA - neurotransmitter function). Oxidized in the cells of the brain tissue with the release of energy stored in the form of ATP. It has the ability to increase the permeability of muscle cells to potassium ions [21].

Clearly, the role of glutamic acid in the activity of cells and tissues is extremely important and attracts the attention of researchers for a long time. In this regard, the search for pharmacological agents capable of directly or indirectly restore the concentration of glutamic acid in the body is important. We therefore, studied the state of glutamate in patients with nosological syntropy and influence of the drug on dino-96 restores the ability of the normal content of glutamic acid in these patients.

The drug is Dino-96 is a natural, mineral and amino acid complex with a rich complex of natural substances. The drug meets the needs of body tissues, since it contains most of the known L-amino acid (20 L-amino acids, including glutamic and), micro-and macro (sodium, potassium, magnesium, calcium, aluminum, barium, cobalt, manganese, lithium, nickel, iron, zinc, copper, cadmium, boron, molybdenum, phosphorus, etc.), fragments of vitamins, hormones and enzymes. Amino acids contained in the substrate, there are other components in its proportions, is only found in nature. Conserve natural stereochemistry, there are no synthetic amino acids. Through the development of the internal molecular structure, the individual components of the substrate are represented as trace elements and are capable of direct penetration into cells, bypassing the typical way: the gastrointestinal tract - liver - circulatory system - cage (of course, abridged).

Materials and methods

Group of the patients consisted of 51 volunteers from the nosological syntropy: patients with combined pathology of the nervous (astenovegetativny syndrome, IRR, 11 circulatory encephalopathy on the background of the stage of cerebral arteriosclerosis, hypertension, stage 11/01), cardiovascular (ischemic heart disease, arrhythmias), food-in satisfactory (chronic gastritis, gastro), hepatobiliary system (biliary dyskinesia, chronic cholecystitis, fatty steatosis). Of those patients in Group 1 (12 people aged 18-29 years) diagnosed: astenovegetativny syndrome, VSD combined with the arrhythmia, chronic gastritis, gastroduodenitis, biliary dyskinesia, chronic cholecystitis. In the second group were 39 patients (aged 47-62 years) with dyscirculatory encephalopathy stage, combined with hypertension, stage coronary artery disease, heart rhythm disturbances, chronic cholecystitis, chronic gepatoheletsistitah, fat hepatitis. The control group consisted of 30 healthy people.

Quantitative indicators of glutamate was determined by the standard method on non-invasive blood analyzer AMP ("BIOPROMIN" UKRAINE) mmol / l in blood, before and 1 hour after a single application of 0,1% solution, Dino 96.
The reliability of the data confirmed statistically.

**Description of the method**

The studies were conducted using non-invasive blood analyzer AMP ("BIOPROMIN", Ukraine). The principle of operation of the analyzer AMP is based on processing of the dynamics of temperature indicators in five biologically active points: the place of carotid bifurcation (left - Shh and TSD - right) in the axillary (T and T aksd aksss) and abdominal (Tabd) fields up to 0,000ºC.

The method is based, laid the theoretical data about the importance of heat transport in the blood and heat transfer communication with the heat capacity (Cv), thermal conductivity (K) defining the mass transfer in open systems. The relationship between man and the environment is realized through changes in heat capacity and thermal conductivity under the influence of external factors (atmospheric pressure, atmospheric gas composition, externalities, psychogenic, physical, chemical). These changes cause a series of one-step reaction between the chemical elements: carbon-nitrogen-hydrogen-oxygen from the heat and transfer it to the circulatory system. In other words, the basic technique is to study the situation of the human relationship with the environment by studying the interaction of the enzymatic and hormonal systems of the hemopoietic system.

Diagnosis is regarded as a typical cybernetic process based on the collection, transmission, storage and processing of gene-fenotipcheskoy information. Information appears under the influence of gas composition, atmospheric pressure and flux of the environment on the organism with the formation of reciprocal temperature and metabolic response to mandatory participation mitogenreguliruyuschego factor (MYFF), transforming growth factor, structural proteins of cell membranes actin spektrina, glycophorin, nitric oxide and arginine. All of this information process is implemented with the participation of chemical elements in the structure of membranes and cell organelles (carbon, hydrogen, nitrogen, oxygen, phosphorus and sulfur) as a result of the interaction of nervous, endocrine, immune and hematopoietic systems at the level of activation of the MYFF. Activation of the MYFF is carried out by tyrosine kinase cascade. MYFF inhibition occurs with the participation trionin-serine complex. As in the activation process and inhibition of the MYFF proteinsotatova involved (5,14,15).

This information is the chemical process of changing the status of the function is controlled genetically MYFF and relationship of carbohydrate, protein and fat metabolism at the level of lysosomes and cytosol of cells with the formation of lysosomal pH 5 and pH 7.35 cytosol determining the normal average temperature of 5 reference points -36.75 ° C. The quality of this information determines the function of the MYFF. The ratio of temperatures 5 biologically active points to 1Tabd normally equal to 5 (1), which corresponds to the ratio of triglycerides in chylomicrons to the number of aminopeptidov in the fat metabolism, which is also equal to 5 (4,9-5,1). The amount of temperature indicators and points 2 Tson 1Tabd normally in the range 99,9 - 100,3 ° C, which is determined by the interaction of proteolytic activity of trypsinogen and its inhibitor in the cell membrane. The above theoretical results are implemented in the program "Success", which is the basis of a screening set of "Non-invasive blood analyzer (AMP)" (22-25)

\[
\text{TSD Shh + T aksd + T aksd} + \text{Tabd/Tabd} 1 = 5 (1)
\]

Studied the relationship of temperature change in the reference points and cellular, biochemical, and other factors have allowed the blood to help the program "Success", to develop a methodology for determining the parameters of homeostasis of the body 117, including glutamic acid.

**Results of the study and discussion**
Found that in patients examined before the drug took place Dino 96 regular decrease in the content of glutamic acid in the blood. The survey data content of glutamic acid in the blood before and after a single application of 10% solution Dino 96 are presented in Table 1.

**Table 1.** The content of glutamate in the blood of patients with nosological syntropy.

<table>
<thead>
<tr>
<th>Groups surveyed</th>
<th>Number of tested</th>
<th>Before use Dino 96 (M ± m)</th>
<th>After the application of Dino 96 (M ± m)</th>
<th>Percentage of normalization of glutamate</th>
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<tbody>
<tr>
<td>Group of 1</td>
<td>12</td>
<td>0,0044 ± 0,00004*</td>
<td>0,0047 ± 0,00001*</td>
<td>100%</td>
</tr>
<tr>
<td>Group of 2</td>
<td>39</td>
<td>0,0042 ± 0,00003*</td>
<td>0,0046 ± 0,00002*</td>
<td>73,4%</td>
</tr>
<tr>
<td>Group Control</td>
<td>20</td>
<td>0,0049 ± 0,00003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
<td></td>
<td></td>
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Note: * - reliability indices when compared with the control group (p <0.05).

In patients of group 1 to of the drug Dino 96 content of glutamate in the blood 0,0044 ± 0,00003 * mmol / l, which is significantly lower than the control group, whereas patients 2 groups of glutamate content 0,0042 ± 0,00003 * mmol / l that a significantly lower and the control groups. After treatment Dino 96 in the first group of the normalization of glutamate was observed in 100% of patients, whereas patients in group 2 normalization of glutamate was noted in 73.4% of cases. The data obtained after treatment corresponded to the lower limit of normal (0,0045-0,0055 mol / L).

1. Given the important role of glutamate tissue metabolites, the violation of its concentration in the blood, may be regarded as one of the pathogenetic factors involved in the formation of a nosological syntropy.

2. Single dose of the drug Dino 96 leads to a significant increase in the concentration of glutamate in the blood. In 74.4% of the patients with nosological syntropy in Group 2 of the normalization of the marker, whereas in patients with functional impairment in a group of recovery of glutamate was determined in 100% of the patients, while the majority of patients, the concentration of glutamate was lower limit of normal.

3. Given the good results once the drug Dino 96, to further explore course of therapeutic effects in various diseases.

4. Studies of glutamate on non-invasive blood analyzer AMP is recommended for quality control of drug therapy of patients syntropy nosology, and in particular drug Dino 96

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Feature of chronic diseases in modern conditions is multifactorial pathogenesis and heterogeneity, due to violation of fundamental regulatory systems of the body. This leads to the weighting of the flow involved in the paired organs involved in the other organs and systems. The medical literature is widely used terms: syntropy, interference, multimorbid denoting the relationship of various diseases among themselves. Syntropy - Two or more pathogenetically related, naturally emerging diseases [1, 2, 3, 4, 5, 6, 7, 8]. While the growth of a multiplicity of diseases with age reflects, above all, involutional processes, the concept of comorbidity - the possibility of a causal combinations thereof, has been studied much less. The problem of combining disease is difficult to perceptsimoe value [9, 10], being one of the most challenging faced by physicians [11]. Along with this nosological syntropy which is important for scientific and practical medicine [12], is particularly relevant in relation to commonly occurring and highly significant social pathologies of the nervous and cardiovascular system, gastrointestinal diseases, and musculoskeletal system. WHO researchers have shown that the conduct of therapeutic and preventive measures are no longer able to change the looming situation and traditional approaches to the treatment of common diseases leading to huge economic losses and modest results (Ivashkin VT, IN Ulanova, 2006). The problem of low efficiency of therapeutic and preventive measures related to the absence of etiological orientation due to insufficient understanding of the key mechanisms of formation of the vast majority of multifactorial diseases (Weiss KM, Terwilliger JD, 2000).

Classes of diseases of the nervous, cardiovascular, digestive system and musculoskeletal system are the most resource-intensive, have a high degree of compatibility and plurality, you visit the hospitals and the duration of hospitalization, primary disability and premature mortality that takes justified their prevention and treatment at the level of one of the priority areas of medicine [13, 14].

Diagnosis in one patient, multiple disease is a characteristic feature of the present patient. The combination of disease increases with age from 1.8 the disease in one person (aged 15-29 years) to 2.4 or more (60 and older) women, these figures are somewhat higher. Nosological syntropy observed in patients with insulin-dependent diabetes, while they are more common chronic relapsing inflammatory processes in different locations. The multiplicity of related diseases - the most important feature of the modern "cardiac" patients [15, 16, 17]. At the heart of syntropy or logical combinations of certain common diseases is their common risk factors and mechanisms of development [15]. Well-known combination of coronary heart disease (CHD) and diabetes mellitus, ischemic heart disease and hypertension, ischemic heart disease and erosive-ulcerous lesions of gastroduodenal zone [15, 17].

Along with this, combined pathology of the nervous, cardiovascular, gastrointestinal neglected. There are no data on the general pathogenetic mechanisms of lymphoma syntropy. Therefore, diagnosis and
therapy of lymphoma syntropy currently remains clinically and socially significant problem. In this regard, search for pharmacological agents acting on the common pathogenetic mechanisms of development of lymphoma syntropy seems relevant.

The literature describes diseases and pathological conditions associated with changes in the level of sulfhydryl (thiol, HS) groups in the body: in particular coronary heart disease and myocardial infarction (TV Alyutova, 1979, 1983), bronchial asthma, (ND. Dzhangulova, 1984), chronic gastroduodenitis and duodenal ulcer (NA Peresugin et al, 1993), late toxicosis of pregnancy (EV Kostyushov, 1984), tonsillitis, diphtheria, infectious mononucleosis, typhoid fever, viral hepatitis, head trauma (MV Aleksandrov, 1979). Adverse environmental factors (laser, magnetic field, physical activity, toxins, allergens, noise) lead to simultaneous changes in the level of reduced and oxidized thiol groups.

Sulfhydrylsoderzhaschie compounds - molecules that contain a part of HS-groups are well represented in the cell in the form of the tripeptide - glutathione, amino acids: Cysteine, cystine, and many proteins. In this case, an important role in antioxidant protection is given by this SH-containing compounds. In the cell, they exist in two states - the reduced (-HS) and oxidized (-SS-). Moreover, the concentration of HS-groups is several times higher concentration of SS-groups, as most of the thiol protein has a physiological activity in the reduced state, and glutathione is a major component of the redox buffer system cells, is maintained in its reductive environment (VN Kulinsky, LS Kolesnichenko, 1990). Sulfhydryl compounds plays a key role in protecting cells from the radical OH. Due to the short half-life and radius of diffusion of OH. in biological systems, this compound is not subject to enzymatic inactivation, and at the same time can have a strong cytotoxic and mutagenic effects, the latter determines the importance of SH-containing compounds - active interceptor OH.-radicals.

Under various stress effects, toxic effects under the influence and enzymatic pathogenicity factors of various infectious agents, including plague, anaerobic gas infection, streptococci groups of staphylococcal bacteria, there is a reversible oxidative modification of SH-groups, leading to an increase in disulfide groups, which is a typical non-specific reaction to the extreme action of the stimulus.

However, the change in the ratio of reduced and oxidized thiol groups in the predominance of recent changes the state of the permeability of cell membranes, their adhesive properties, resulting in a dramatic inhibition of the function of sulfur-containing enzymes or coenzymes (lipoic acid, coenzyme A, glutathione), disruption of thiol metalloproteins (cytochrome P-450 ), a number of hormone receptors and transcription factors, protein thiol.

Thiol proteins are involved in virtually all of the key biochemical processes: in energy metabolism, ion exchange, conducting nerve impulses to muscle contraction, at the reception, etc. [17,18,19]. It is well known that oxidation of the thiol groups of membrane proteins may lead to non-enzymatic reaction of SH-groups of lipids with free radicals, with formation of sulfhydryl radicals, which then interact with the formation of disulfides or oxidized by oxygen with the formation of sulfonic acid derivatives:

\[
\begin{align*}
    \text{Pr-SH} + \text{L} & \rightarrow \text{LH} + \text{Pr-S} \\
    \text{Pr1-S} + \text{Pr2-S} & \rightarrow \text{Pr1-SS-Pr2} \\
    \text{Pr-S} + \text{O}_2 & \rightarrow \text{Pr-SO}_2 \rightarrow \text{ sulfonic acid derivatives}
\end{align*}
\]

Large role in the pathology of the cell is also inactivation of ion-transport enzymes in the active site thiol group which includes, first of all Ca2 +-ATPase. Inactivation of these enzymes leads to a slowdown, "pumping" of calcium ions from the cells and, conversely, to the entrance of calcium into the cell, which leads to an increase in intracellular calcium ion concentration and cell damage. Finally, the oxidation of
thiol groups of membrane proteins leads to defects in the lipid layer of cell membranes and mitochondria. Under the influence of electrical potential difference across the membranes of such pores in the cell are sodium ions, and in the mitochondria - the potassium ions. The result is an increase in osmotic pressure within cells and mitochondria and swelling. This leads to more damage to the membrane:

1. To change the properties of the lipid layer
2. Increase in the microviscosity of membranes
3. Reduce the amount of hydrophobic
4. Increasing the polarity of the lipid phase
5. Change the surface charge of membranes and lipoproteins
6. Increase in permeability to hydrogen ions
7. Increase in permeability to calcium ions

Increased permeability to calcium ions is the second result of lipid peroxidation due to the fact that the products of peroxidation are capable of directly increasing the ionic permeability of the lipid layer. It is established that the products of lipid peroxidation do the lipid phase of membranes permeable to hydrogen ions and calcium. This leads to the fact that mitochondrial oxidation and phosphorylation disunite, and the cell is in terms of power hunger (ie, lack of ATP). At the same time go out to the cytoplasm, calcium ions, which damage cell structures. The third (and perhaps most important), the result is a decrease in the stability of peroxidation of the lipid layer, which can lead to electrical breakdown of the membrane's own membrane potential, ie under the influence of electrical potential difference that exists in the membranes of living cells electrical breakdown, leads to complete loss of membrane barrier function.

In the 60 years was completed numerous clinical studies have shown that a variety of diseases cause the same reaction - lowering the concentration of HS-groups in the serum of patients. The degree of reduction of the concentration of these groups depended on the severity of the disease: the more severe clinical disease is expressed, the lower the level of HS-groups in blood serum. Similar in character changes were identified in the study of the influence of various factors on human and animal organisms (cold, emotional stress, magnetic field, exercise, etc.) [17]. In 1979, V. Sokolowski speculated about the existence of a single tioldisulfidnoy system (thiols exist in the cell in two forms - the reduced and oxidized), and nonspecific adaptive reactions are of great importance vzmoprevrascheniya these forms (2-HS ↔ SS+2 H •).

Circulatory disorders of the organs and tissues, the development of hypoxia, decreased energy cells, acidosis, change in the conformation of membrane proteins, impaired membrane permeability, occurs when the overwhelming number of diseases. Developing due to occlusion ischemia causes oxidative stress in the development of which play an important role metabolic disorders caused by the damaging effect of reactive oxygen species (ROS), which runs uncontrolled lipid peroxidation of biological membranes. And thus, to protection against toxic effects of reactive oxygen species provides antioxidant system (AOS), a sensitive non-enzymatically component of which are thiol groups.

Clearly, the role of thiol compounds in the life of cells and tissues is extremely important and attracts the attention of researchers for a long time and the search for pharmacological agents that could restore the thiol group of patients with multiple organ pathology is important. In this regard, the influence of the drug Dino-96’s ability to restore the thiol groups of patients with nosological syntropy is relevant.

The drug is Dino-96 is a natural, mineral and amino acid complex with a rich complex of natural substances. The drug meets the needs of body tissues, since it contains most of the known L-amino acid (20 L-amino acids, including cysteine and containing SH-groups), micro-and macro (sodium, potassium, magnesium, calcium, aluminum, barium, cobalt, manganese, lithium, nickel, iron, zinc, copper, cadmium, boron, molybdenum, phosphorus, etc.), fragments of vitamins, hormones and enzymes.
Amino acids (components of protein) contained in the substrate, there are other components in its proportions, is only found in nature. Conserve natural stereochemistry, there are no synthetic amino acids. Through the development of the internal molecular structure, the individual components of the substrate are represented as trace elements and are capable of direct penetration into cells, bypassing the typical way: the gastrointestinal tract - liver - circulatory system - cage (of course, abridged). Individual amino acids are represented not as a whole, as well as fragments of a human body and are selected as a substitute for that part of the diseased tissue, which was damaged or diseased. Before the drug Dino-96 in the body normalizes the process of self-regulation, regeneration and homeostasis.

Thiols play an important role of tissue antioxidants, since sulfhydryl groups are highly reactive, easily oxidized, it protects cell components from damage, manifesting as antiradical and antiperoxide action.

The purpose of this study was to examine changes in the content of thiol groups (SH-groups), the blood of patients with nosological syntropy and assess single-use drug Dino 96.

**Description of the method**

The studies were conducted using non-invasive blood analyzer AMP ("BIOPROMIN", Ukraine). The principle of operation of the analyzer AMP is based on processing of the dynamics of temperature indicators in five biologically active points: the place of carotid bifurcation (left - Shh and TSD - right) in the axillary (T and Taksd akss) and abdominal (Tabd) fields up to 0,000°C.

The method is based, laid the theoretical data about the importance of heat transport in the blood and heat transfer communication with the heat capacity (Cv), thermal conductivity (K) defining the mass transfer in open systems. The relationship between man and the environment is realized through changes in heat capacity and thermal conductivity under the influence of external factors (atmospheric pressure, atmospheric gas composition, externalities, psychogenic, physical, chemical). These changes cause a series of one-step reaction between the chemical elements: carbon-nitrogen-hydrogen-oxygen from the heat and transfer it to the circulatory system. In other words, the basic technique is to study the situation of the human relationship with the environment by studying the interaction of the enzymatic and hormonal systems of the hemopoietic system.

Diagnosis is regarded as a typical cybernetic process based on the collection, transmission, storage and processing of gene-fenotipcheskoy information. Information appears under the influence of gas composition, atmospheric pressure and flux of the environment on the organism with the formation of reciprocal temperature and metabolic response to mandatory participation mitogenreguliruyuschego factor (MYFF), transforming growth factor, structural proteins of cell membranes actin spektrina, glycophorin, nitric oxide and arginine. All of this information process is implemented with the participation of chemical elements in the structure of membranes and cell organelles (carbon, hydrogen, nitrogen, oxygen, phosphorus and sulfur) as a result of the interaction of nervous, endocrine, immune and hematopoietic systems at the level of activation of the MYFF. Activation of the MYFF is carried out by tyrosine kinase cascade. MYFF inhibition occurs with the participation trionin-serine complex. As in the activation process and inhibition of the MYFF proteinfosfotazy involved (5,14,15).

This information is the chemical process of changing the status of the function is controlled genetically MYFF and relationship of carbohydrate, protein and fat metabolism at the level of lysosomes and cytosol of cells with the formation of lysosomal pH 5 and pH 7.35 cytosol determining the normal average temperature of the reference points 5, 36, 75 ° C. The quality of this information determines the function of the MYFF. The ratio of temperatures 5 biologically active points to 1Tabd normally equal to 5 (1), which corresponds to the ratio of triglycerides in chylomicrons to the number of aminopeptidov in the fat metabolism, which is also equal to 5 (4,9-5,1). The amount of temperature indicators and points 2 Tson
1Tabd normally in the range 99.9 - 100.3 °C, which is determined by the interaction of proteolytic activity of trypsinogen and its inhibitor in the cell membrane. The above theoretical results are implemented in the program "Success", which is the basis of a screening set of "Non-invasive blood analyzer (ILA)" (22-25).

TSD Shh + T asd + T akss + 1Tabd/1Tabd 1 = 5 (1)

Studied the relationship of temperature change in the reference points and cellular, biochemical, and other factors have allowed the blood to help the program "Success", to develop a methodology for determining the 117 blood parameters that characterize the basic parameters of homeostasis, including thiol groups.

The reliability of the data confirmed statistically.

Materials and methods

Group of the patients consisted of 51 volunteers from the nosological syntropy: patients with combined pathology of the nervous (astenovegetativny syndrome, IRR, circulatory encephalopathy on the background of the stage of cerebral arteriosclerosis, hypertension, 1–11 stage cardiovascular (ischemic heart disease, arrhythmias), food-in satisfactory (chronic gastritis, gastro), hepatobiliary system (biliary dyskinesia, chronic choleductitis, chronic hepatoduodenitis, fatty steatosis). Of those patients in Group 1 (12 people aged 18-29 years) diagnosed: astenovegetativny syndrome, VSD combined with the arrhythmia, chronic gastritis, gastroduodenitis, biliary dyskinesia, chronic choleductitis. In the second group were 39 patients with encephalopathy diitsirkulyatorny 11stage, combined with hypertension1–11stage, coronary artery disease, heart rhythm disturbances, chronic choleductitis, chronic hepatoduodenitis, fatty steatosis. The control group consisted of 20 healthy people.

Quantitative indicators of thiol groups was determined by the standard method on non-invasive blood analyzer AMP ("BIOPROMIN" UKRAINE) mmol / l in blood, before and after 1 hour 5posle single application of 0,1 % solution, Dino 96. The reliability of the data confirmed statistically.

Results of the study and discussion

Found that in patients examined before the drug took place 96 Dino regular decrease in the content of thiol groups in the blood. The survey data content of thiol groups in blood before and after a single application of 10% solution Dino 96 are presented in Table 1.

Table 1.
The content of thiol groups in the blood of patients with nosological syntropy.

<table>
<thead>
<tr>
<th>Groups surveyed</th>
<th>Number of tested</th>
<th>Before use Dino 96 (M ± m)</th>
<th>After the application of Dino 96 (M ± m)</th>
<th>Percentage of normalization of SH-groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group of 1</td>
<td>12</td>
<td>6,030 ± 0,229 *</td>
<td>6,820 ± 0,497 *</td>
<td>33,3 %</td>
</tr>
<tr>
<td>Group of 2</td>
<td>39</td>
<td>5,313 ± 0,586 *</td>
<td>6,596 ± 0,502*</td>
<td>2,5 %</td>
</tr>
<tr>
<td>Group Control</td>
<td>20</td>
<td>7,356 ± 0,005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Note: * - reliability indices when compared with the control group (p <0.01)

In patients of group 1 to of the drug Dino 96 content of thiol groups in the blood of 6,030 ± 0,229 * mol/l, which is significantly lower than the control group, whereas the 2 groups of patients the content of thiol groups of 5,313 ± 0,586 * mol/l significantly below 1 and the control group. After treatment Dino 96 in the first group content of thiol groups - 6,820 ± 0,497 * mol/ L, the second group of 6,596 ± 0,502 * mol / l. Full restoration of the content of thiol groups in the blood of persons of group 1 occurred in 4 (33.3%) patients, whereas in group 2, the normalization of the marker occurred in 1 (2.5%). But the rest of the patients 1 and 2 levels of groups of the thiol groups after treatment significantly increased Dino96, but did not reach the lower limit of normal (7,32-7,4).

CONCLUSIONS

1. Given the important role thiol compounds in metabolic processes, reducing the concentration of thiol groups may be regarded as one of the pathogenetic factors involved in the formation of a nosological syntropy. It is concluded that the definition of HS-groups can be an integral indicator of adaptive capacity of the organism and its non-specific resistance in patients with nosological syntropy. Reducing the concentration of thiol groups in these patients indicates a decline in adaptive abilities of the organism, its non-specific resistance and antioxidant protection.

2. Single dose of the drug Dino 96 leads to increased concentrations of thiol groups in the blood. However, in most cases, patients with nosological syntropy not reach the standards.

3. Given the good results once the drug Dino 96, to further explore course of therapeutic effects in various diseases.

4. Non-invasive blood analyzer AMP can be used to examine the contents of HS-blood groups in patients nosological syntropy in the treatment of drug-Dino-96 and can be recommended for dynamic observation of the pharmacotherapy of other drugs.

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