



Medicines based on coordination compounds of iron and other microelements for the treatment of anemia

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Abstract. Today, the Republic pays special attention to the production of chemical industry products and their implementation in the economic sectors. Based on the development strategy of the Republic of Uzbekistan, aimed at "further modernization and diversification of industry by transferring it to a qualitatively new level, aimed at the accelerated development of high-tech manufacturing industries, primarily in the production of finished products with high added value based on deep processing of local raw materials", "development of the production of fundamentally new types of products and technologies" the most important tasks are defined. In this aspect, the development of leading sectors of the national economy, including the chemical industry, obtaining new ligands based on a given organic synthesis and the use of complex compounds of d-metals based on them, is an urgent task.

Key words: "Cosmofer", "Feromaks", "Ferrumlek", "Maltofer", "Coamida", "Cupramide".

Introduction. Currently, the pharmaceutical market of Uzbekistan is one of the dynamically developing sectors of the national economy, and the range of antianemic drugs is quite wide. However, the analysis of pricing and assortment policy in the market of antianemic drugs showed that it is necessary to take measures to develop and introduce into production domestic substances and dosage forms, as well as diversify domestic production by developing assortment varieties and introducing import-substituting products. As is known, the Tashkent Pharmaceutical Institute carries out targeted synthesis of drugs based on coordination compounds of biometals. Cobalt plays a critical role in the endogenous synthesis of vitamin B12 (cyanocobalamin), which is involved in the synthesis of hemoglobin. Its deficiency causes pernicious anemia and is accompanied by a decrease in antitumor immunity. It is recommended as a means of stimulating leukopoiesis in secondary leukopenia occurring during chemoradiation therapy of malignant tumors, in pathology of the blood and hematopoietic organs. Ascorbic acid is a powerful antioxidant. Vitamin C strengthens the human immune system and protects it from viruses and bacteria, affects the synthesis of a number of hormones, regulates hematopoiesis and normalizes capillary permeability, participates in the synthesis of collagen protein, regulates metabolism, removes toxins, improves bile secretion, restores the exocrine function of the pancreas and thyroid gland. The initial stage of the study of bioavailability is the determination of the release time of the drug from the dosage form. It has been established that the solubility test, as a first approximation, characterizes the bioavailability of the drug (since it is an instrumental method for determining the bioavailability of the drug), since in



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practice there is a very frequent correlation between the rate of dissolution and absorption. Dissolution in in vitro experiments is an important instrumental method for studying the biopharmaceutical quality of drugs.

The prevalence of iron deficiency and manifest stage of iron deficiency anemia (IDA) in the countries of Central Asia, including Uzbekistan, is extremely high, exceeding the WHO critical level by 1.5-2 times and ranks first among general morbidity.

The Government of the Republic of Uzbekistan and the Ministry of Health of the Republic of Uzbekistan pay special attention to the problem of IDA, which is reflected in the implementation of the program for the mass prevention of iron deficiency states - this is the "National Program for the Fortification of Flour with Iron", "National Program for Weekly Iron Supplementation in Risk Groups", "Program for the Development of National Nutrition Policy", etc. The manifest form of IDA develops after a period of latent iron deficiency due to the gradual depletion of iron reserves, which is most often explained by insufficient iron and vitamin B12 (or their absence) in the diet, as well as a deficiency of folic acid. IDA in combination with B12 - folate deficiency anemia is anemia of mixed genesis and is quite common in our region.

Main part. Iron in the human body can be divided into two large groups: cellular and extracellular. Intracellular iron compounds are divided into 4 subgroups: 1 - hemoproteins, the main structural element of which is heme (hemoglobin, myoglobin, cytochromes, catalase and peroxidase); 2 - iron-containing enzymes of the non-heme group (succinate dehydrogenase, acetyl coenzyme, NADPH - cytochrome C reductase, etc.); 3 - ferritin and hemosiderin of internal organs; 4 - iron loosely bound to proteins and other organic substances.

Extracellular iron compounds include iron-binding proteins – transferrin and lactoferrin, contained in extracellular fluids. The iron content in the body of an adult is from 4 to 5 g and is distributed as follows: 70.5% in hemoglobin, 3.2% in myoglobin, 26% in the form of reserve compounds of ferritin and hemosiderin, etc. According to modern concepts, the main role of iron in the body is the formation of hemoglobin, which is necessary for the respiratory function of the blood. It is the iron of the prosthetic group of hemoglobin, which is in a complex with a specific protein – globin, that is able to reversibly attach oxygen without changing its valence (+2). Divalent iron is absorbed much better than trivalent iron. Almost all iron is in the form of organic complexes, so iron metabolism is a transformation of its complexes.

It is known that it is impossible to stop iron deficiency anemia without iron preparations only by a diet consisting of iron-rich foods. Treatment of iron deficiency anemia should be carried out with iron preparations, and the appointment of vitamins B6 and B12 with their sufficient content is not justified. Iron preparations for internal use are numerous, but not all of them are equally effective and well tolerated. Currently, mainly divalent, ferrous iron compounds are used, since it is absorbed much better. The absorption of iron preparations is enhanced in the presence of ascorbic and succinic acid. Iron included in complex compounds is well absorbed. As literary data show, the pharmacotherapeutic group for the treatment of hematopoietic pathologies is most widely represented by complex compounds. For example, feramide and ferrocere tablets, a cobalt phytate analogue – a phytin complex with Fe (II) – ferrophytin, pyrofer – an iron (III) compound with pyridoxine, etc. Recently, the drug forms of the drug “FerrumLek” have found wide application for the treatment of hematopoietic disorders – solutions for intramuscular and intravenous injections, 100 mg tablets, syrup and drops. Iron in these drug forms is bound in a complex of iron



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(III) hydroxide with polymaltose and therefore does not form insoluble compounds with food components such as phytin, oxalate ion, tannin, as well as drugs – tetracycline and antacids.

The paper studies the effect of a copper, manganese, cobalt, iron, and titanium microelement complex (CMC) and a copper, manganese, cobalt, iron, titanium, and folic acid complex (MAF) in various ratios on the regeneration of blood composition in dogs after bloodletting and on the restoration of peripheral blood composition in rabbits with experimental phenylhydrazine anemia. It is shown that the introduction of microelements against the background of developed phenylhydrazine anemia accelerated the restoration of the number of erythrocytes and hemoglobin in experimental animals.

Bala Yu. M. and co-workers present a summary of long-term observations concerning changes in the level of metals in the hematopoietic organs, blood cells and their structures, plasma and its fractions. It has been shown that in posthemorrhagic anemia and leukemia, zinc saturation of erythrocytes increases, with a simultaneous decrease in the concentration of chromium and molybdenum in the components of the blood. The use of individual metals for therapeutic purposes in long-term hematological diseases is recommended. The features of the balance of iron, cobalt, copper and zinc, as well as the provision of the body with ascorbic and nicotinic acids in anemia in children have been studied. It has been shown that in deficiency anemia, a negative balance of iron and cobalt develops, as well as PP-vitamin and C-vitamin deficiency, the frequency and intensity of which are directly dependent on the severity of the disease. Terekhov et al. have shown that the use of the iron-containing drug "Ferro-gradumet" ensures the maintenance of normal iron and transferrin levels throughout the entire treatment period and rapid restoration of blood counts in patients with posthemorrhagic anemia.

The work studied a large number of iron-containing drugs for the treatment of IDA in children. It was found that for young children, the following are preferable: Antiferrin, Maltofer, FerrumLek, and Hemofer; for adolescents, FerrumLek, Tardiferon, and Ferrogra-dumet, which are well tolerated by patients. Kalmenov G.T. studied the effectiveness of using some antianemic drugs: Ferroplex, Tardiferon, and FerrumLek (iron III). It was found that the use of all drugs demonstrated a pronounced therapeutic effect, but the greatest increase in hemoglobin, serum iron, and ferritin was observed with the use of FerrumLek.

M.A. Aripov studied the comparative effect of the preparations "Feramida", "Coamida" and "Cupramide" on the peripheral blood picture in posthemorrhagic and phenylhydrazine anemia. It was found that an increase in the amount of hemoglobin and erythrocytes was accompanied by an increase in the number of reticulocytes, which indicates enhanced regeneration of bone marrow hematopoiesis under the influence of a mixture of preparations. A.I. Iskandarov and his colleagues studied the effect of the preparation "Zinc-50" (a coordination compound of zinc with histidine) on the peripheral blood picture in posthemorrhagic anemia. It was found that the preparation promotes an increase in weight, hemoglobin content and the number of erythrocytes. Complexes of iron, cobalt, zinc, copper and gold with vitamins PP and B6 with glycerol, histidine are known, which turned out to be effective antianemic, hypolipidemic, antituberculosis agents and introduced into medical practice: feramide, coamide, cupir and pyracin. The effect of feramide in combination with pyrogenal in viral hepatitis B with concomitant iron deficiency anemia has been studied. Biochemical indices of ferritin and transferrin content in blood serum have been studied in the dynamics of the disease. It has been established that the use of feramide and pyrogenal in the



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complex treatment of patients with hepatitis B with concomitant IDA promotes normalization of biochemical indices, restoration of ferritin and transferrin in blood serum and reduction of terms of clinical recovery. E.A. Nazarov proposed the preparations "Feraskofol" and "Mumifer" for the treatment of anemia, containing feramide, coamide, ascorbic acid and mumiyo. Methods for the quantitative determination of the main ingredients of tablets using atomic absorption spectrometry were developed.

The quality assessment and standardization of Ferascfol were carried out. Methods for the qualitative and quantitative determination of biologically active substances of the drug were developed. The method of high-performance liquid chromatography (HPLC) was used to identify the active substances. The analysis was carried out on an Agilent technologies 1100 liquid chromatograph in the isocratic mode on a Zorbax Eclipse XDB C-18 column measuring 3.0 x 150 mm, with a particle size of 3.5 μm . The advantage of this method is the simultaneous determination of both active substances and nicotinamide impurity. H.K. Bekchanov et al. studied the bioavailability of Ferascfol tablets in vitro and in vivo experiments, and proved the possibility of using the in vitro method under manufacturing conditions instead of in vivo. Absorption characteristics were assessed using the Dissolution test. The development of the "Dissolution" test for Ferascfol tablets was carried out in stages for iron: at the first stage, the choice of conditions for dissolving medicinal substances (device, temperature, pH of the dissolution medium, mixing mode, method for determining the content of the medicinal substance in the dissolution medium) was scientifically substantiated; at the second stage, the dissolution standards were determined: the amount of the active substance released by a certain point in time and the time during which a certain amount of the active substance is released from the dosage form; at the third stage, the reliability of the dissolution standards selected at the second stage, the methods for determining some pharmacokinetic parameters of the medicinal substance by the in vivo method and finding parameters that correlate with the data of the in vitro method were controlled.

The optimum stirring mode for Ferascfol tablets was established – 100 rpm and the optimum dissolution time was 30 min. It was shown that under these conditions at least 78% of iron passes into solution.

The effectiveness of the antianemic drug Globex was studied. It contains divalent iron (ferrous fumarate) – 304 mg, folic acid – 1.5 mg, vitamin B12 (in gelatin) – 10 mcg, elemental zinc – 15 mg. Studies have shown that under the influence of the drug Globex, erythropoiesis indices improve – the amount of hemoglobin and erythrocytes increases, and an increase in reticulocytes was observed.

The work studied the effectiveness of the semi-functional antianemic drug Globex for the treatment of patients with anemia. A significant impairment of erythropoiesis in non-pregnant and pregnant women with anemia has been established – the content of serum iron, energy supply of the body and activity of the enzyme SDH are significantly reduced. The use of the drug "Globex" has shown its pronounced effectiveness, as evidenced by the growth of the number of reticulocytes, erythrocytes, hemoglobin. Under the influence of the drug, SDH increases and energy-synthetic processes improve.

The use of the drug "Tardiferon" as a therapeutic agent [91] showed its good restorative and corrective ability, which allows us to consider it an optimal effective drug. Under the influence of pathogenetic treatment with tardiferon, the indices of erythropoiesis significantly improved. The



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authors studied the efficiency of the prolonged-release drug "Ginotardiferon" in the treatment of anemia. "Ginotardiferon" contains folic acid, the need for which increases significantly in anemia. The presence of folic acid provides protection of the gastrointestinal tract from the direct effects of biometal (iron), improves tolerance and ensures better absorption of the drug. Tukhtayev K.R. and Turakhodzhaeva S.S. studied the efficiency of "Ayustan" and "Maltofer", as well as their combined administration on the state of bone marrow hematopoiesis in rats with experimental anemia. It has been established that the combination of Maltofer and Ayustan effectively restores the blood picture, which allows them to be recommended for the complex treatment of anemia. A comparative study of Ferropir with Ferrum-lek has been conducted. It has been established that the average daily increase in hemoglobin and serum iron in Ferropir is lower than in Ferrum-lek. Ferropir has a weaker antianemic effect. Amonov I.I. and Vorozheikin V.M. studied the effect of Maltofer and ascorbic acid on the morphofunctional state of erythrocytes in iron deficiency anemia. It has been established that under the influence of Maltofer and ascorbic acid, the properties of the membrane (elasticity, flexibility and deformability) in erythrocytes improve, leading to an increase in the functional activity and vital activity of formed elements of the blood. The work [99] presents the results of a comparative analysis of the effectiveness of treating anemia in women using the drugs "Maltofer" and "Ginotardiferon". As a result of the treatment, it was established that the drug "Maltofer" is more effective in treating postpartum anemia in women and is preferable for treating IDA.

Strigaleva Z.M. and her colleagues studied the effectiveness of using the drug "Maltofer" for the treatment of mild IDA (hemoglobin level 90-110 g/l). The treatment aimed at eliminating mild iron deficiency by using the drug "Maltofer" turned out to be effective and the drug is recommended as monotherapy for mild IDA. Akhmina N.I. and Okhlopkova K.A. prescribed ferrotherapy for IDA for prophylactic or therapeutic purposes in combination with folic acid. The group of iron preparations included "Ginotardiferon", "Maltofer" and "Aktiferrin", which have proven themselves to be effective in IDA. It was established that the problem of providing vitamins and microelements is closely related to the problem of rational nutrition. In the work [102], the effectiveness of the domestic drug "Ayustan" in the treatment of IDA was studied. The conducted studies have shown that under the influence of the drug, there is an improvement in protein-forming function and a more pronounced antianemic effect.

The authors studied the therapeutic efficacy of "Maltofer" and "Ferlatum" in IDA. It was found that both drugs provide regression of clinical symptoms of IDA, an increase in the hemoglobin level, normalization of red blood cell counts and iron metabolism indicators. At the same time, when using "Maltofer", normalization of hemoglobin and ferritin status occurs faster than when using "Ferlatum", which is associated with a higher dose of elemental iron in the first drug.

The effectiveness of treating IDA with the drug "Ferro-folgamma" (Germany) was studied. It was shown that the drug is well tolerated by patients with long-term use, effective for the treatment and prevention of IDA.

The authors showed that even mild anemia leads to pathological changes in the placenta. The drug "Ferro-folgamma" is recommended in obstetric practice for the prevention and treatment of anemia, including its mild forms.

Various iron preparations for the treatment of IDA were studied in a comparative aspect: gemostimulin, ferramide, iron sulfate, ferroplex, ferrogradumet, venofer, tardiferon, fenyuls,



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sorbifer, ferronat, etc. Of all the iron-containing preparations studied, only "Fenyuls" did not have any adverse effects. The preparation "Fenyuls" contains 45 mg of iron (II), 50 mg of ascorbic acid, 2 mg of riboflavin, 2 mg of vitamin B6 and 2.5 mg of pantothenic acid.

Pospelova T.I. with co-workers studied, along with iron preparations (Aktiferrin, Tardiferon and Sorbifer), pantohepatogen, which is a substance of the blood of the Altai maral and contains a complex of biologically active substances: amino acids, microelements, lipids, nucleotides, etc. It was shown that the inclusion of pantohepatogen in the treatment of IDA improves the condition of patients and leads to rapid normalization of red blood cell counts. Abdullina L.R. with co-workers studied the effect of the drug Sorbifer Durules on the dynamics of clinical and laboratory parameters and the state of free radical oxidation of lipids in young patients with IDA. It was established that combination therapy with the inclusion of the antioxidant β -carotene, in contrast to isolated iron therapy, leads to a reliable improvement in the clinical picture, iron metabolism parameters and lipid peroxidation processes, and to an increase in the hemoglobin level. In terms of early prevention and treatment of IDA, there is currently a wide range of iron-containing drugs, such as Gino-tardiferon, Apofer, FerrumLek, Aktiferrin, Maltofer, Hemofer, Venofer, Sorbiferdureles, Ferronat, etc. There is some experience in treating with the above drugs. In this regard, the question arises of choosing an effective, safe and affordable iron preparation for children and women. Therefore, research is ongoing to develop more effective iron-containing drugs. The conducted analysis of the pricing policy of antianemic (iron-containing) drugs registered in the Republic of Uzbekistan, according to price segments, showed that domestic drugs are in the lowest price range (1000-5000 soums), which ensures their availability to the population and their share of antianemic drugs in circulation is 44%. The drug "Maltofer", used to treat anemia in children, and "Ginotardiferon", which is in demand for the treatment of anemia in pregnant women, represent the price segment of 5,000-10,000 soums (35%). "Ferlatum" and "Cosmofer" are representatives of the price range of 10,000-50,000 soums (11%). A tendency has been revealed to reduce the assortment of drugs "Gemofer", "Globex", "Ferrocal", "Ferask", with a simultaneous increase in the number of offers of rather expensive drugs "Cosmofer", "Feromaks", "Ferrumlek", "Maltofer", therefore it is necessary to take measures to develop and introduce into production domestic substances and dosage forms, as well as diversify domestic production by developing assortment varieties and introducing import-substituting products.

Conclusion. Analysis of the literature showed that a fairly large number of works are devoted to the synthesis and physicochemical study of new coordination compounds of microelements with bioactive substances, but only a small number of them are developed and introduced into medical practice, therefore, studies aimed at creating new drugs and dosage forms that affect regional pathology (anemia, leukopoiesis, atherosclerosis, vitiligo, etc.) are very relevant.

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