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TUBERCULOSIS AND IRON-CONTAINING CHEMOTHERAPEUTIC DRUGS

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ABSTRACT

Today, in our country, special attention is paid to improving the healthcare system, including early diagnosis, treatment and prevention of tuberculosis.Some features of iron metabolism in mycobacteria are considered, as well as the varieties and pathogenesis of various variants of anemia that can develop with tuberculosis: iron deficiency (subcutaneous iron deficiency), associated with chronic disease (with relative iron deficiency) or drug-induced (variants: sideroachrestic, hemolytic, aplastic). The possibilities of correction of tuberculosis treatment regimens with the introduction of a complex compound of iron with isoniazid in order to reduce undesirable adverse reactions to isoniazid are analyzed.

Introduction.Some studies in several countries showed that old age, positive acid-fast bacilli (AFB) smear of sputum, severity of chest radiograph, presence of pneumonia,Diabetes Mellitus (DM), low albumin level, sepsis, and multiorgan failure were the mortality predictor factors in pulmonary TB with acute respiratory failure.This study aimed to analyse factors that predict mortality in active pulmonary TB patients with respiratory failure. Tuberculosis as a chronic disease is often accompanied by the development of anemic syndroma, that is, a decrease in the level of hemoglobin and/or erythrocytes per unit volume of blood [1]. In addition, anemia in tuberculosis patients may be associated with both concomitant diseases and hematotoxic effects of anti-tuberculosis chemotherapy. According to the pathogenesis, anemia in tuberculosis can be iron-deficient (with absolute iron deficiency), associated with a chronic disease (with relative iron deficiency) or drug-induced [1]. The risk of anemia increases in the case of comorbidity of tuberculosis and HIV infection [2].To review the literature over the past 15 years on the study of iron metabolism in tuberculosis to determine the possibilities of using iron-containing chemotherapeutic drugs in its treatment.

RESULTS AND DISCUSSION

In the domestic and foreign literature there are many fundamental works devoted to the exchange of iron, which is an essential

trace element not only for the human body, but also for some microorganisms, including Micobacterium tuberculosis (MBT) [3, 4, 5, 6]. The independent variables were age, AFB sputum smear results, thorax radiographic findings, concomitant pneumonia, sepsis, hypoalbuminemia, and DM. The dependent variable was mortality rate. Follow-up was carried out until two weeks after participating patients were discharged from the hospital. Average standard intersection was used for continuous data. Mortality predictor factors were analyzed using Chisquare continue with multivariate logistic regression to obtain the mortality predictor factor model. The result was presented in Odds Ratio (OR) with a significant p-value of <0.05 and a confidence interval (CI) of 95%.Demographic data and patients' characteristics were descriptively presented in frequency and percentage for categorical data. More than 20 proteins have been described that exchange iron and maintain its homeostasis; the most important are transferrin, ferritin, ferroportin, ferroxidases and the hormone hepsidin [7, 8, 9, 10, 11]. Hepcidin is a hormone that blocks the functions of ferroportin (the only exporter of iron from cells), which leads to the accumulation of intracellular iron pool and prevention of the toxic effect of free iron [12, 13]. Microorganisms, unlike humans, have a system of special iron carriers from the environment surrounding the bacterium into the cell – siderophores, which extract iron and metalloproteins and hemoproteins [14, 15, 16].Disorders of iron metabolism in tuberculosis can

be caused not only by the interaction of macro- and micro-organism and the presence of concomitant diseases, but also by the hematotoxic effect of anti-tuberculosis drugs [15].

There are pathogenetic variants of drug-induced anemia in humans: sidereoachrestic, hemolytic, aplastic [1].Sideroachrestic, or iron-saturated, anemia develops when there is a sufficient level of iron in the body and it is impossible for the bone marrow to use it for hemoglobin synthesis. Hydrazide preparations

isonicotinic acid (isonioside /(GINK)), pyrazinamide and cycloserine, used for the treatment of tuberculosis, cause a deficiency of pyridoxal phosphate, a cofactor in heme synthesis reactions. With insufficient heme synthesis, iron is not utilized, but accumulates in sideroblasts, then in internal organs. The administration of pyridoxine (B6) against the background of anti-tuberculosis_ therapy levels the deficiency of pyridoxal phosphate [1,17, 18].Hemolytic anemia is associated with shortening the lifespan of red blood cells and their pre-premature disintegration. Anti-tuberculosis drugs can cause hemolysis by various mechanisms. Nonimmune hemolysis occurs extremely rarely in patients with congenital deficiency of glucose-6-phosphate dehydrogenase of erythrocytes under the action of isonioside, sodium para-aminosalicylate (PASC), ethionamide, protionamide, levofloxacin. Immune hemolysis occurs more often and develops according to the immunocomplex mechanism; it is associated with the action of PASC, rifampicin, less often – isoniazid [1].Another variant of drug-induced anemia is aplastic, or partial, red cell aplasia. It can be caused by isoniazid, PASC, linezolid, which have a direct toxic effect on

the progenitor cells of erythrocytes [1, 19]. Various pathogenetic variants of anemia are associated with different groups of anti-tuberculosis drugs, but the most aggressive drug that can lead to hematological complications is isoniazid [4, 8, 17, 19, 20]. In the works of Gritsenko N.S., Dolgikh V.T., a decrease in the contractile function of the myocardium was experimentally proved in rats by the action of isoniazid [21].

Complex iron-containing preparations based on isoniazid are also described in foreign literature. In particular, the antitubercular complex Na3 [Fe(CN) 5 (isoniazid)] (IQG607) is of interest due to its ability to overcome resistance. IQG607 has the potential for redox activation, in which the radical acylpyridine (isonicotinoyl) can be generated without the help of the mycobacterial enzyme katG. Studies of the reactivity of the complex by electron spectroscopy

it showed a very high rate of oxidation of bound isoniazid, more than 460 times higher than the oxidation of free isoniazid. The obtained effect allows the complex compound to exhibit bacteriostatic properties against some isoniazid-resistant strains of MBT [22, 23]. In 2009, a group of Russian scientists developed an anti-tuberculosis drug isonicotinoyl hydrazine iron sulfate (phenazide), which is a chelated complex of isoniazide and ferrous iron. It provides greater safety of tuberculosis chemotherapy, since the iron-blocked chelate node of the hydrazine molecule of isonicotinic acid (GINK) loses its ability to interact with the active centers of metal-containing enzymes, and the inclusion of the primary amino group of hydrazine in the chelate cycle of the complex prevents interaction with N-acetyltransferase. Metabolism of the complex compound of GINK and iron sulfate,

unlike isoniazid, it follows the path of oxidation, not acetylation, and toxic metabolites are not transformed. In this rgard, phenazide is a low-toxic drug, the use of which does not require correction of single and course doses of the drug, depending on the rate of its acetylation. It has no effect on the central nervous system, does not have an immunotoxic and allergenic effect. In addition, a complex preparation, including iron, has

a preventive and curative effect in the case of iron deficiency [24, 25, 26, 27]. The active substance of phenazide is isoniazide. Microbiological studies in vitro have shown comparable efficacy of phenazide and isoniazide.Comprehensive studies of the drug included: a study of the comparative effectiveness of phenazide and isoniazide; determination of the bioavailability of phenazide in patients with tuberculosis; study of the clinical efficacy, tolerability of phenazide and the effect on iron metabolism in the patient's body, the risk of hemosiderosis [24].

The study of the bioavailability of phenazide was conducted on the basis of the Volgograd Medical Academy.The study included 2 groups of patients with newly diagnosed pulmonary tuberculosis. The calculation of the bioavailability of the compared drugs showed that the same clinical efficacy of phenazid and isoniazid in the daily dose of phenazid is explained by its higher bioavailability (the bioavailability of the latter was 220% relative to isoniazid) [24].

The effect of phenazide as an iron-containing drug on red blood parameters was studied on the basis of the Novgorod

regional Tuberculosis dispensary.The study included 2 groups of patients: 36 people received phenazid in a daily dose of 500 mg as one of the main anti-tuberculosis drugs, 40 people received isoniazid in a daily dose of 600 mg. In half of the patients of the first group, before the start of therapy, deviations in red blood indicators were detected, which during treatment with phenazide (hemoglobin level, red blood cell count, color index) reached normal values. In the group of patients receiving isoniazid, a similar trend was not observed [24].In the studies of Mishina A.V., Mishina V.Yu., Mitrushkina V.I. et al., 2013-2018, the comparative effectiveness of the chemotherapy regimen with the inclusion of phenazide and standard chemotherapy mode in combination with ART in HIV-infected patients with newly diagnosed pulmonary tuberculosis in the intensive phase was studied. In the group of patients with HIV infection and newly diagnosed pulmonary tuberculosis, the highest efficiency of there is a chemotherapy regimen with the inclusion of phenazide. Among patients treated with phenazide in combination with other drugs, the rates of bacterial excretion cessation and cavern closure were 70% and 40%, respectively. Among patients who received a standard chemotrerapy regimen without phenazide, the rates of bacterial release cessation and cavern closure were 20% and 7.5%, respectively [28, 29, 30]. The effectiveness of treatment of patients with pulmonary tuberculosis who received chemotherapy regimens with phenazide was 81.4%, which is comparable to the effectiveness of regimens including isoniazid (85.7%) [31]. There are data on the inclusion of phenazide in the treatment regimens of pregnant women and maternity women with tuberculosis, which is associated with the absence of irreversible adverse reactions and better tolerance of phenazide compared with isoniazide [32].

Conclusion

The clinical picture of tuberculosis is accompanied by many syndromes, among which is anemic syndrome. Anemia in tuberculosis can develop in the form of anemia of chronic diseases, iron deficiency anemia or be a hematotoxic complication of anti-tuberculosis chemotherapy, which is quite rare and is associated primarily with the queue with the reception of isoniazid.Currently, in the treatment regimens of tuberculosis, instead of isoniazid, it is possible to prescribe isonicotinoyl hydrazine iron sulfate (phenazide), which has less toxicity and the ability to correct iron deficiency conditions.

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