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TUBERCULOSIS AND IRON-CONTAINING CHEMOTHERAPY DRUGS

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

Keywords: tuberculosis; diagnostics, mycobacteria; metabolism of iron isoniazid; ftivazid

Introduction

Some studies in several countries have shown that advanced age, a sputum smear test positive for acid-resistant bacilli (CB), chest X-ray severity, the presence of pneumonia, diabetes mellitus (DM), low albumin levels, sepsis and multiple organ failure were factors predicting mortality in pulmonary tuberculosis with acuterespiratory failure. . The aim of this study was to analyze the factors predicting mortality in patients with active pulmonary tuberculosis with respiratory failure. Tuberculosis as a chronic disease is often accompanied by the development of anemic syndrome, that is, a decrease in the level of hemoglobin and / or red blood cells per unit volume of blood [1]. In addition, anemia in patients with tuberculosis can be associated with both concomitant diseases and the hematotoxic effects of anti-tuberculosis chemotherapy. According to the pathogenesis, anemia in tuberculosis can be iron deficiency (with absolute iron deficiency), associated with chronic disease (with relative iron deficiency) or medication [1]. The risk of developing anemia increases with a combination of tuberculosis and HIV infection [2]. Conduct a review of the literature for the last 15 years on the study of iron metabolism in tuberculosis to determine the possibility of using iron-containing chemotherapeutic drugs in its treatment. care.

Results and Discussion

In domestic and foreign literature, there are many fundamental works on the exchange of iron, which is an essential trace element not only for the human body, but also for some microorganisms, including Mycobacterium tuberculosis (MBT) [3, 4, 5, 6]. The independent variables were age, SPUTum smear results at KUM, chest X-ray data, concomitant pneumonia, sepsis, hypoalbuminemia, and diabetes mellitus. The dependent variable was the mortality rate. Follow-up was carried out within two weeks after the participating patients were discharged from the hospital. The mean standard intersection was used for continuous data. mortality predictor factors were analyzed using Chisquare. continue multivariate logistic regression to obtain a model of the mortality predictor factor. The result was presented as a odds ratio (OR) with a significant p-value of < 0.05 and a confidence interval (CI) of 95%. Demographic data and patient characteristics were descriptively presented in frequency and percentage for categorical data. More than 20 proteins were described that exchange iron and maintain its homeostasis; the most important are transferrin, ferritin, ferroportin, ferroxidases and the hormone hepcidine [7, 8, 9, 10, 11]. Hepsidin is a hormone that blocks the functions of ferroportin (the only exporter of iron from cells), which leads to the accumulation of an intracellular pool of iron and prevents the toxic effects of free iron [12, 13]. Microorganisms, unlike humans, have a system of special carriers of iron from the environment surrounding the bacterium into the cell – siderophores, which extract iron, metalloproteins and hemoproteins [14, 15, 16]. Iron metabolism disorders in tuberculosis can be caused not only by the interaction of macro- and microorganisms and the presence of concomitant diseases, but also by the hematotoxic effect of anti-tuberculosis drugs [15].

There are pathogenetic variants of human drug anemia: sideroachrestic, hemolytic, aplastic [1]. Sideroachrestic, or iron-saturated, anemia develops when there is a sufficient level of iron in the body and the impossibility of its use by the bone marrow for the synthesis of hemoglobin. Hydrazide preparations isonicotinic acid (isonioside / (GINK)), pyrazinamide and cycloserine, used to treat tuberculosis, cause a deficiency of pyridoxal phosphate, a cofactor of heme synthesis reactions. With insufficient synthesis of heme, iron is not utilized, but accumulates in sideroblasts, then in the internal organs. The introduction of pyridoxine (B6) against the background of anti-tuberculosis __ therapy eliminates the deficiency of pyridoxal phosphate [1,17, 18]. Hemolytic anemia is associated with shortening the life of red blood cells and their premature disintegration. Anti-TB drugs can cause hemolysis by various mechanisms. Non-immune hemolysis occurs extremely rarely in patients with congenital deficiency of glucose-6-phosphate dehydrogenase of erythrocytes under

the action of isonioside, sodium paraamine salicylate (PASK), ethionamide, protionamide, levofloxacin. Immune hemolysis occurs more often and develops according to the immunocomplex mechanism; it is associated with the action of PASK, rifampicin, less often - isoniazid [1]. Another variant of drug anemia is aplastic, or partial, erythrocyte aplasia. It can be caused by isoniazid, PASK, linezolid, which have a direct toxic effect on erythrocyte precursor cells [1, 19]. Different 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 in rats under the influence of isoniazid was experimentally proved [21].

In foreign literature, complex iron-containing preparations based on isoniazid are also described. In particular, the anti-tuberculosis 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 acylpyridine (isonicotinyl) radical can be formed without the help of the mycobacterial enzyme katG. Studies of the reactivity of the complex by electron spectroscopy have shown a very high oxidation rate of bound isoniazid, more than 460 times higher than the oxidation rate of free isoniazid. The resulting effect allows the complex to exhibit bacteriostatic properties against some isoniazid-resistant strains of MBT [22, 23]. In 2009, a group of Russian scientists developed the anti-tuberculosis drug isonicotinylhydrazine ferrous sulfate (phenazide), which is a chelated complex of isoniazid and ferrous iron. Provides greater safety of tuberculosis chemotherapy, since the iron-blocked chelated node of the hydrazine molecule isonicotinic acid (GINK) loses its ability to interact with the active sites 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. The metabolism of the complex compound HINK and ferrous sulfate, unlike isoniazid, follows the path of oxidation, rather than acetylation, and does not transform into toxic metabolites. In this regard, 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. Does not affect the central nervous system, does not have an immunotoxic and allergenic effect. In addition, a complex preparation that includes iron has a preventive and therapeutic effect in iron deficiency [24, 25, 26, 27]. The active substance of phenazide is isoniazid. Microbiological studies in vitro showed comparable efficacy of phenazide and isoniazid. Comprehensive studies of the drug included: the study of the comparative efficacy of phenazide and isoniazid; the determination of the bioavailability of

phenazide in tuberculosis patients; the study of clinical efficacy, tolerability of phenazide and the effect on iron metabolism in the patient's body, the risk of developing 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 phenazide and isoniazid in the daily dose of phenazide is explained by its higher bioavailability (the bioavailability of the latter was 220% in relation to isoniazid) [24].

The effect of phenazide as an iron-containing drug on red blood indicators was studied on the basis of the Novgorod Regional Anti-Tuberculosis Dispensary. The study included 2 groups of patients: 36 people received phenazide in a daily dose of 500 mg as one of the main anti-tuberculosis drugs, 40 people received isoniazid at a daily dose of 600 mg. Half of the patients of the first group before the start of therapy revealed deviations in red blood parameters, which, against the background of treatment with phenazide (hemoglobin level, number of red blood cells, color index) reached normal values. In the group of patients treated with isoniazid, a similar trend was not observed [24]. In the studies of Mishina A.V., Mishina V.Yu., Mitrushkin V.I. et al., 2013-2018, a comparative effectiveness of the chemotherapy regimen with the inclusion of phenazide and the standard chemotherapy regimen in combination with ART in HIV-infected patients with newly diagnosed pulmonary tuberculosis in the phase of intensive treatment was carried out. Studied. In the group of patients with HIV infection and newly diagnosed pulmonary tuberculosis, the chemotherapy regimen with the inclusion of phenazide is most effective. Among patients treated with phenazide in combination with other drugs, the frequency of cessation of bacterial excretion and closure of caverns was 70% and 40%, respectively. Among patients treated with a standard chemotherapy regimen without phenazide, the frequency of bacterial excretion cessation and cavern closure was 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 is evidence of the inclusion of phenazide in the treatment regimens of tuberculosis patients in pregnant women and women in labor, which is associated with the absence of irreversible adverse reactions and better tolerability of phenazide compared to isoniazid [32].

Conclusion

The clinical picture of tuberculosis is accompanied by many syndromes, including 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 for taking isoniazid. Currently, in the treatment regimens for tuberculosis, instead of isoniazid, iron isonicotinylhydrazine can be prescribed instead of isoniazid. sulfate (phenazide), which has less toxicity and the ability to correct iron deficiency states.

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