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Negative Effects of Antituberculous Drugs for Patients with Combination of Tuberculosis and Covid-19

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Abstract: Hepatobiliary system of patients with tuberculosis suffers by different reasons: tuberculous intoxication, taking of antituberculosis drugs with high hepatotoxic activity, joining coronavirus infection. The purpose of our research was a study of structure of hepatotoxic reactions at children and adolescents, consumptive at combination with a coronavirus infection (SARS CoV - 2). Materials and methods: 26 children and adolescents are inspected with tuberculosis of intrathoracic lymphatic nodes in the stage of infiltration, treatings in the Samarkand center of phthisiology and pulmonology.

In a basic group (I) 13 is plugged patients with the confirmed concomitant coronavirus infection of SARSCoV - 2, in the group of comparison (II) – 13 patients by tuberculosis of children and adolescents without by a concomitant Sars-CoV-2. In the process of treatment with antituberculosis preparations children and adolescents with combination of tuberculosis and coronavirus infection the side effects of drugs on a liver, gall-bladder and spleen were observed approximately 3,7 time more frequent, than in a group with the isolated tuberculosis. Side toxic effect of antituberculosis drugs in I to the group of children were educed on a 15 twenty-four hours before from the beginning of therapy, their relapses were registered in 1,8 time more frequent. For patients by tuberculosis with combination of Sars-Cov-2 toxic influence of drugs on a liver resulted in more heavy flow of side effects : often educed clinically, obviously there was violation of structure of cages of hepatic parenchima, more frequent found out the phenomena of cholestasia, to portal hypertension, in addition a change took place in fabrics of pancreas. In addition stagnation and increase was more frequent registered pressure in the portal system of vessels; violation of motor activity of gall-bladder.

Keywords: tuberculosis, Sars-CoV-2, children, hepatotoxic reactions.

The problem of the negative impact of drugs with anti-tuberculosis activity on the human hepatobiliary system is still relevant today. When tuberculosis co-occurs with some viral diseases, the problem of preventing functional and structural liver disorders arises, and this in turn can lead to undesirable side reactions during and after anti-tuberculosis treatment [1,3]. In cases where tuberculosis occurs simultaneously with coronavirus infection (SARS CoV-2), a number of researchers have identified functional and organic damage in the organs of the hepatobiliary system (HBS), which created a negative effect and affected the effectiveness of treatment of a specific process and required the need for correction of anti-tuberculosis therapy [4] . Only thanks to the work of the organs of the hepatobiliary system, its barrier and

disinfecting functions, about 85% of toxic substances are removed from the human body. The hepatobiliary system in patients with tuberculosis suffers for various reasons: tuberculosis intoxication, taking anti-tuberculosis drugs with high hepatotoxic activity, associated coronavirus infection (SARS CoV-2) [5,6]. However, early detection of hepatotoxic reactions is difficult, since these reactions do not manifest themselves clinically, but are diagnosed only through biochemical studies [2].

Purpose of the study: studying the structure of hepatotoxic reactions (GTR) in children and adolescents with tuberculosis in combination with coronavirus infection (SARS CoV-2).

Materials and methods. To analyze the structure and characteristics of GAD, a complete study of the organs of the GBS was performed in 26 children and adolescents with tuberculosis of the intrathoracic lymph nodes in the infiltration stage, treated at the Samarkand Center for Phthisiology and Pulmonology. The main group (I) included 13 patients with confirmed concomitant coronavirus infection SARS CoV-2, the comparison group (II) included 13 children and adolescents with tuberculosis without concomitant coronavirus infection. In group I there were 7 boys and 6 girls, in group II there were 9 and 4, respectively. The average age of patients in group I was 6.2 ± 3.5 years, in group II – 9.9 ± 2.4 years. Both groups of patients received similar anti-tuberculosis therapy. At the time of our study, patients in both groups were in the hospital and were undergoing an intensive phase of treatment. We analyzed clinical examination data, biochemical data: (alanine aminotransferase (ALT), aspartate aminotransferase (AST), ALT and AST ratio, total bilirubin, direct and indirect bilirubin, alkaline phosphatase (ALP), cholinesterase (ChE)) blood and ultrasound data of the liver and gallbladder. Statistical processing of the obtained data was carried out using the Statistica 8.0 program. The arithmetic value and the root-mean-square error of the mean value are estimated: – X±m. The significance of differences in indicators and relative frequency values in independent samples was assessed using Student's t-test; differences between indicators were considered significant at $p < 0.05$.

Research results. Some patients complained of manifestations assessed as hepatotoxic, which made it possible to identify the side effects of drugs on the liver even before laboratory confirmation. In group I, compared with patients in group II, a decrease in appetite was more often observed (5 - 45.5% and 1 - 33.3%), pain and a feeling of heaviness in the right hypochondrium (7 - 63.6% and 1 - 33.3%), nausea (8 – 72.7% and 1 – 33.3%), statistical significance $p < 0.05$ was noted between groups.

Studying the data of a biochemical blood test in patients upon admission to our medical institution, we found that in patients of group I the levels of ALT, AST, ChE and amylase were higher than normal, in patients of group II the same data were within normal limits (Table 1). We found statistically significant differences between both groups in terms of cholinesterase and amylase: higher rates in group I compared to group II – 68.61 ± 4.72 μmol/min × l versus 50.69 ± 3.02 μmol/min × l and 72.09 ± 10.03 U/L versus 51.22 ± 10.99 U/L, respectively.

Table 1. Biochemical blood test data in patients of both groups before treatment

Groups		AST, units/l	ALT/AST, conventionalunits	ChE, μmol/min×l	Amylase, units/l
Group I (n=13)	70.88 ± 8.33	56.64 ± 8.77	0.77 ± 0.07	68.61 ± 4.72*	72.09 ± 10.03*
Group II (n=13)	50.22 ± 6.41	39.12 ± 6.32	0.79 ± 0.04	50.69 ± 3.02	51.22 ± 10.99
Normal indicators	8.0-54.0	16.0-40.0	1.33	30.0-60.0	10.0-96.0

*Note: * - statistically significant differences between groups (p<0.05)*

During sonography of the liver, gallbladder and spleen, as well as their vessels, we found that in group I, hepatomegaly, an increase in the vertical size and thickness of the right lobe of the liver (in 86.5% versus 25.5%), and structural disturbances were observed more often than in group II. liver parenchyma (in 2–15.4% and in 1 – 7.7%), an increase in the anatomical size of the spleen (in 4 – 30.8% and in 2 – 15.4%), disruption of the structure of the pancreas (in 3 – 23.1% and 1 -

7.7%), as well as an increase in the diameter of the cystic duct and splenic vein, these data were statistically significant - $p < 0.05$.

Sonography of the pancreas in patients of both groups revealed that an increase in the average size of the organ in group I occurred significantly more often (9–69.2%) than in group II (3–23.1%) ($p<0.05$) .

In patients of both groups, when treated with anti-tuberculosis drugs, adverse hepatotoxic reactions were recorded: in 11 (84.6%) patients of group I and only in 3 (23.1%) patients of group II ($p < 0.05$). In Table 2, we reflected the comparative indicators of hepatotoxic reactions in both groups of patients: in group I, early onset of side effects of drugs, a greater number of relapses of toxic reactions, as well as an increase in the length of time required to eliminate such undesirable manifestations of anti-tuberculosis therapy were more often noted ($p < 0.05$).

Table 2. Comparative indicators of hepatotoxic reactions in both groups of patients during anti-tuberculosis therapy

Groups	Duration of development of the first adverse reaction, days	Frequency of episodes of adverse reactions (abs.)	Duration of relief of adverse reactions, days
Group I (n = 13)	26.23 ± 4.77*	4.31 ± 0.88*	15.51 ± 3.76*
Group II (n = 13)	39.66 ± 5.71	2.55 ± 0.59	8.33 ± 3.98

*Note: * - statistically significant differences between groups ($p < 0.05$)*

In patients from both groups, side effects of anti-tuberculosis therapy on the liver were expressed in the death of liver cells, bile stagnation, and disturbances in various functions of the liver and pancreas.

Table 3. Dynamics of adverse reactions to the liver and pancreas in patients of both groups

Deadlines	Groups of patients	ALP, units/l	ChE, μmol/min ×l	ALT, units/l	AST, units/l	ALT/AST, conventionalunits	Total BR, μmol/l	PBR, μmol/l	NBR, μmol/l
At the beginning of therapy	Group I (n = 13)	277.96 ± 33.4	35.29 ± 4.64	288.41 ± 16.87	101.72 ± 7.99	0.72 ± 0.03	17.77 ± 3.45	4.71 ± 0.15	11.65 ± 3.22
	Group II (n=13)	212.19 ± 25.33	57.31 ± 3.99	120.82 ± 12.51	75.20 ± 6.38	0.38 ± 0.05	15.16 ± 3.48	1.41 ± 0.14	6.77 ± 4.01
At the end of therapy	Group I (n = 13)	30.65 ± 4.93	25.33 ± 3.83	50.03 ± 7.14	37.11 ± 3.46	0.88 ± 0.04	8.99 ± 2.66	0.88 ± 0.05	8.51 ± 1.81
	Group II (n=13)	48.32 ± 4.77	45.12 ± 3.77	28.90 ± 4.46	27.13 ± 5.66	0.97 ± 0.09	5.61 ± 0.74	0.73 ± 0.07	3.21 ± 0.82

Note: statistically significant differences were $p < 0.05$

When assessing biochemical blood parameters to analyze the side effects of drugs that arose at the beginning of treatment, almost all data (except ChE) in group I were significantly higher ($p < 0.05$), and the level of ChE was significantly lower than in patients of group II .

By the end of anti-tuberculosis therapy, patients in group I who experienced adverse toxic reactions during treatment had only significantly ($p < 0.05$) high levels of ALT and significantly low levels of ChE.

Conclusion. During treatment with anti-tuberculosis drugs, sick children and adolescents with a combination of tuberculosis and coronavirus infection, side effects of drugs on the liver, gall bladder and spleen were observed approximately 3.7 times more often than in the group with isolated tuberculosis (in 11/13 (84.6%) and in 3/13 (23.1%) patients, respectively) ($p<0.05$).

Side toxic effects of anti-tuberculosis drugs in group I children were identified 15 days earlier from the start of therapy, their relapses were recorded 1.8 times more often. In patients with tuberculosis with a combination of coronavirus infections, the toxic effect of drugs on the liver led to a more severe course of side effects: often detected clinically, a violation of the structure of cells of the hepatic parenchyma was clearly observed, phenomena were detected more oftencholestasis, portal hypertension, in addition, there was a change in the tissues of the pancreas.

In patients with tuberculosis in combination with coronavirus infection, at the beginning of therapy with anti-tuberculosis drugs, such phenomena as inflammation, tissue swelling and an increase in the anatomical size of the liver and pancreas are reliably often detected as toxic effects. In addition, stagnation and increased pressure in the portal vascular system were more often recorded; impaired motor activity of the gallbladder.

By the end of the course of anti-tuberculosis therapy in children with a combination of tuberculosis and coronavirus infection, disorders of the liver parenchyma cells, stagnation of bile in the bladder, as well as a decrease in the anatomical size of the liver and spleen were reliably often detected.

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