THE USE OF ISONIAZID SYRUP FOR THE PREVENTION OF TUBERCULOSIS IN CHILDREN

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Summary

The purpose of the study was to conduct a comparative analysis of the use of isoniazid in the form of syrup and tablet for the prevention of tuberculosis in children.

Materials and methods. 114 children at risk who were on sanatorium treatment at Chernivtsi children's sanatorium (Ukraine) were examined for tuberculosis. For chemoprophylaxis in children the drug "Isoniazid" was used: 61 children received the drug in the form of syrup (group 1), 53 - in tablet form (group 2). On the basis of Institute of Pneumology "Marius Nasta" (Romania) 83 children enrolled to the 1 group received preventive therapy with isoniazid in the form of syrup.

Results. Significantly lower levels of total protein were reported in 1 group - by 9.6% than in patients in 2 group ($p<0.05$). Also significantly higher levels of bilirubin - by 17.2 %, ALT (alanine transaminase) - by 19 %, AST (aspartate transaminase) - by 22.4 % and thymol test - by 15.5 % were reported in 2 group compared with 1 group ($p <0.05$), evidencing that there are preconditions for the development of toxic hepatitis when using isoniazid in tablet form. It is well established that the changes in blood chemistry were much more pronounced in children who received isoniazid tablets and were increasing up to the completion of the course of chemoprophylaxis.

Conclusions. The results of complex clinical, laboratory and instrumental study allow us to recommend "Isoniazid" in the form of syrup 100 mg / 5 ml as highly effective drug for the prevention of tuberculosis in children.

Key-words: tuberculosis, treatment, isoniazid, syrup, children.

Rezumat. **Utilizarea izoniazidei sirop pentru prevenirea tuberculozei la copii**

Scopul studiului a fost efectuarea unei analize comparative a utilizării izoniazidei sub formă de sirop și de comprimate pentru prevenirea tuberculozei la copii.

Materiale și metode. 114 de copii din grupa de risc care se aflau la tratament în sanatoriul pentru copii din Cernăuți (Ucraina) au fost examinați în vederea depistării tuberculozei. Pentru chimioprofilaxie la copii a fost utilizat medicamentul „Izoniazidă": 61 de copii au primit medicamentul sub formă de sirop (grupa 1), 53 – sub formă de comprimate (grupa 2). La baza Institutului de Pulmonologie „Marius Nasta" (România), 83 de copii înscriși în grupa 1 au primit tratament preventiv cu izoniazidă sub formă de sirop.

Rezultatele. Au fost înregistrate nivele scăzute a proteinelor totale în grupa 1 (diferența cu indicatorii grupului 2 a fost de 9,6%, ($p <0,05$)). În grupa 2 au fost înregistrate nivele ridicate de bilirubină – cu 17,2%, ALT (alanin transaminaza) – cu 19%, AST (aspartat transaminaza) – cu 22,4% și testul de timol – cu 15,5%, în comparație cu grupa 1 ($p < 0,05$), ceea ce indică prezența condițiilor pentru dezvoltarea hepatitei toxice, în cazul utilizării izoniazidei sub formă de comprimate. S-a constatat că schimbările în compoziția chimică a sângelui au fost mai pronunțate la copiii cărora li s-au administrat comprimate de izoniazidă, existând tendința de creștere a acestor indicatori până la finalizarea cursului de chimioprofilaxie.

Concluzii. Rezultatele unui studiu cuprinzător clinic, de laborator și instrumental ne permit să recomandăm Izoniazida sub formă de sirop 100 mg/5 ml ca medicament foarte eficient pentru prevenirea tuberculozei la copii.

Cuvinte-cheie: tuberculoză, tratament, izoniazidă, sirop, copii.

Резюме. Использование сиропа изониазида для профилактики туберкулеза у детей

Целью исследования было проведение сравнительного анализа применения изониазида в форме сиропа и таблеток для профилактики туберкулеза у детей.

Материалы и методы. 114 детей из группы риска, которые находились на санаторно-курортном лечении в Черновицком детском санатории (Украина), были обследованы на туберкулез. Для химиопрофилактики у детей использовался препарат «Изониазид»: 61 ребенок получал препарат в виде сиропа (группа 1), 53 - в виде таблеток

(группа 2). На базе института пульмонологии «Мариус Наста» (Румыния) 83 ребенка, зачисленные в группу 1, получали профилактическую терапию изониазидом в виде сиропа.

Результаты. Были зарегистрированы низкие уровни показателя общего белка в группе 1 (разница с показателями группы 2 составляла 9,6%, (p <0,05)). Зарегистрированы высокие уровни билирубина - на 17,2%, ALT (аланина трансаминазы) - на 19%, AST (аспартат трансаминазы) - на 22,4% и тимолового теста - на 15,5% в группе 2 по сравнению с группой 1 (p<0,05), что свидетельствует о наличии предпосылок для развития токсического гепатита при использовании изониазида в таблетированной форме. Установлено, что изменения в химическом составе крови были более выраженными у детей, получавших таблетки изониазида, наблюдалась тенденция увеличения этих показателей к моменту завершения курса химиопрофилактики.

Выводы. Результаты комплексного клинического, лабораторного и инструментального исследования позволяют рекомендовать «Изониазид» в виде сиропа 100 мг/5 мл как высокоэффективный препарат для профилактики туберкулеза у детей.

Ключевые слова: туберкулез, лечение, изониазид, сироп, дети.

Introduction. One of the main factors for the control of epidemic situation of tuberculosis is an effective treatment for patients that contributes to the improvement of the epidemiological situation as a whole as there is a rupture of the epidemic chain in addition to cure a particular case [1, 6].

According to several authors, carrying out a full chemotherapy, especially when using standard techniques, may be limited by the development of adverse reactions on anti-TB drugs, which occur mainly in the first weeks of intensive phase of chemotherapy [3]. Obviously, this is due to the adaptation of the body to the drug, as well as to the fact that the infiltrative phase of tuberculosis process is a stage of an allergic adjustment of the body and it enhances the non-specific allergy to anti-TB drugs (ATBD) [1,3]. Adverse reactions rate in the application of the standard modes of anti-TB treatment is 10-15%. It has to be refused from further application of anti-TB drugs in 4% of cases. Further correction of the normal chemotherapy regimen associated with AR is often followed by an extension of the basic course of treatment, that has a negative effect on patients' preference of the treatment [4]. All of the above requires thinking in terms of the application of effective drugs with modification of routes of their administration.

Isoniazid is particularly active against strains of TB bacilli, which multiply rapidly and are located in the walls of the cavity in the oxygen-rich environment at neutral pH. Isoniazid inhibits DNA-dependent RNA polymerase and inhibits the synthesis of mycolic acid of mycobacterium tuberculosis cell wall (MTB). The drug has bacteriostatic and bactericidal action against MTB - their growth is contained at the concentration of isoniazid 0.03 μg/ml. M. tuberculosis and *M. bovis* are highly sensitive to isoniazid, but the latter has little effect on pathogens of other infectious diseases. The drug is well absorbed in the gastro-intestinal tract, easily penetrate through the blood-brain barrier into the spinal fluid, pleural effusion, ascites fluid, sputum, saliva, lungs, skin, caseous masses. Time-to-peak blood concentration (T_{max}) is 4-1 hours. Plasma protein binding is 10%. Volume of distribution is 0.56–0.76 l/kg. Tuberculostatic concentration is maintained for 6-24 hours after administration of a single dose. It crosses the placenta and is excreted in breast milk. It is metabolized in the liver by acetylation. Its rate is genetically determined and depends on the level of activity of N-acetyltransferase. There are "fast" and "slow" inactivators depending on the rate of acetylation. The isoniazid half-life is 0.5-1.6 hours in the "fast" inactivators, and the amount of unchanged substance excreted renally is less than 10% per day. 2-5 hours in the "slow" inactivators and more than 10% per day respectively. In newborn the half-life is 7.8-19.8 hours, in children aged 1.5 to 15 years old - 2.3-4.9 hours. It is excreted renally mostly as inactive metabolites: Within 24 hours 75-95% of the dose administered is excreted with urine, a small amount is excreted with faeces [4].

It should be noted that the ARs of toxic nature are actually induced by both the anti-TB drugs itself and their breakdown products. These reactions usually have organ nature and result from an irritant or necrotizing effects on the organs and systems. Such reactions are more common in respect of the digestive system, in particular hepato-pancreato-biliary (HPB) [5].

Thus, the effective management of TB prevention in children due to the use of drugs with high antimycobacterial action of various drug forms is one of the priorities in terms of TB control at all levels of health care.

Table 1

Children population, who annually need phthisiopulmonary care in the Chernivtsi region for 2012-2016 years

No.	Diagnosis	2012		2013		2014		2105		2016	
		under 14 years of age	15-17 years of age	under 14 years of age	15-17 years of age	under 14 years of age	15-17 years of age	under 14 years of age	15-17 years of age	under 14 years of age	15-17 years of age
1.	Patients with active tuberculosis	12	7	9 including 1 – miliary tuberculosis	3	4	6 including 1 XDR TB	7+1 re-currence	6	1	2
2.	Residual changes after previous tuber-culosis, cat. 5.1	46	18	33	16	42	13	31	10	28	7
3.	Contact with pa-tients:										
	- excreting MTB as 5.2 (A);	225	51	199	33	181	40	184	45	160	33
	- excreting MTB as 5.2 (B);	103	50	114	30	109	21	69	12	20	12
4.	Tuberculin skin test conversion cat 5 gr 5.4 (A)	1741	186	1063	108	1457	23	1562	24	1234	8
5.	Patients tubinfected with other precipi-tating causes	1048	103	566	61	637	18	546	11	560	14
	Total	**3175**	**415**	**1984**	**251**	**2430**	**121**	**2400**	**129**	**2003**	**76**
	Total	**3590**		**2235**		**2551**		**2529**		**2079**	

Object. To conduct a comparative analysis of the use of isoniazid in the form of syrup and tablets for the prevention of tuberculosis in children at risk.

Materials and methods. According to the analysis of children population, who annually need phthisiopulmonary care in the Chernivtsi region (*Table 1*), there is a decrease in the identification of children at risk by 30%, in the detection of tuberculosis in the early stages, the deterioration of the structure of clinical forms in diagnosed patients (tuberculous meningitis, miliary tuberculosis in children are reported practically each year). In previous years such forms were reported at intervals 1 per 5 years. For the first time in the history of the Bukovina region it is has been reported a case of multi-drug resistant tuberculosis in children. The results of epidemiological analysis evidence the need for chemoprophylaxis of tuberculosis in children at risk twice a year for three months.

Thus, the analysis of the data presented in Table 1 allowed to select 114 children of TB-related risk groups from different regions of the Chernivtsi oblast who were receiving prophylactic isoniazid: 61 children of them received the drug in the form of syrup (group 1), 53 - in tablet form (group 2). 83 children enrolled to the 1 main study group received preventive therapy with isoniazid in the form of syrup on the basis of Institute of Pneumology "Marius Nasta" (Romania), the control group included 53 children (group 2).

"Isoniazid" of domestic manufacturers was mainly used in children for chemoprophylaxis: in tablet form and isoniazid in syrup. The latter is increasingly used in pediatric practice.

A comparative study of the efficacy and harmlessness of the syrup form of "Isoniazid" (100 mg/5 ml) was carried out in 114 people included to the main group, in accordance with the requirements of the State Pharmacological Center of the Ministry of Health of Ukraine for such studies. The control group included 53 children (group 2). The study was carried out by open-comparative, parallel clinical trial. The boys were 76%, girls - 24%. The mean age was (11.7 ± 1.4) years. Patients in the main group received isoniazid - syrup in a dose of 10 mg/kg (or 0.5 ml/kg) once a day after breakfast daily for 6 months. Patients in the control group received "Isoniazid" as the reference drug in tablets (0.5-3 tablets of 100 mg, depenging on the body weight) once a day after breakfast daily for 6 months.

The therapeutic doses of isoniazid are well tolerated. Side effects in the main group on both bases of the study were not reported. Patients in the control group showed in rare cases (5 people) dizziness, nausea, vomiting, gastritis; sometimes - fatigue, head-

ache, sleep disorders; 7 children - anxiety. In some cases (4) there were skin rash, pruritus, eosinophilia, increase in body temperature.

Before including the child in the study there was assessed the following information collected and recorded in the individual registration form: demographics (gender, age), physical (height, weight), medical history (life and disease), the results of clinical examination (examination of the patient, palpation, percussion, auscultation), blood pressure (BP), heart rate (HR), body temperature (t°), laboratory (complete blood count, general urinalysis, blood chemistry), if necessary - X-ray (plain chest radiography, tomography) and microbiological (bacterioscopy and culture of sputum or epithelial lining fluid for MTB). Patients and their parents (guardians) gave informed consent to participate in research and then adequately cooperated with the medical staff for the entire duration of chemoprophylaxis and control examination. Observation and examination were carried out in a staged manner: screening (the first 2-3 days of admission to a sanatorium) and the entire treatment period (180 days): 1-3, 15, 30, 45, 60, 90 and 180 days. Frequency of researches and data recording was carried out in accordance with the protocol of the scientific research. All examination data were recorded in the sanatorium and health resort card form and/or the individual registration form.

The control of the functioning of the hepatobiliary system was carried out in the study groups according to the abdominal ultrasound examination and the results of routine laboratory biochemical study (total protein, bilirubin, liver enzymes tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), the De Ritis Ratio (AST/ALT ratio)) urea, creatinine). Normal values of Ritisa children are 0.8-1.2.

It was conducted a survey for each child's tolerability of various forms of "Isoniazid" for the prevention of tuberculosis.

Assessment of efficacy was carried out using the above criteria according to generally accepted scale for efficacy: the drug is effective - the drug is ineffective. Signs scale was graduated according to their severity: 0 - absence of sign; 1 - low severity, or just the presence of a sign (in case of gradation "there is/no"); 2 - moderate severity; 3 - significant severity.

Tolerability was assessed according to the objective data on the tolerability scale (tolerability: good, satisfactory, unsatisfactory). Tolerability was assessed on the basis of subjective complaints and sensations of the patient and objective data collected by the researcher. We take into account the dynamics of laboratory parameters, as well as the incidence and nature of adverse reactions. Particular attention was paid to the following signs: nausea, vomiting, digestive disturbance, irritability, anxiety, dizziness, headache, euphoria, sleep disorders, paresthesia, palpitations, allergic (eosinophilia, pruritus and skin rash, increase in body temperature), peripheral neuritis, psychosis.

The analysis of the received data was performed with software packages "STATISTICA " version 10.0.228.8 (StatSoft Inc., USA) on PC, using parametric and non-parametric methods of calculation. Differences between results were considered reliable with $p<0.05$.

The research work is carried out at the expense of the state budget. State registration №0114U002473 "Pathogenetic peculiarities of forming systemic inflammatory response syndrome in extended form of chemoresistance pulmonary tuberculosis improving diagnosis, optimization treatment program and prevention".

Results. The analysis of the assessment of clinical signs of intoxication syndrome (IS) given in the Table 2, showed that slight IS was present both in group 1 and in group 2 at the beginning of chemoprophylaxis, in 33.3% of patients in group 1 and in 36.7% of pa-

Table 2

Assessment of the severity of intoxication syndrome in the study groups at the beginning of chemoprophylaxis and in the dynamics of treatment

The severity of intoxication syndrome	Group 1 (n = 114)		Group 2 (n = 106)	
	Prior to chemoprophylaxis	After chemoprophylaxis	Prior to chemoprophylaxis	After chemoprophylaxis
	%	%	%	%
No	12.3	71.7	13.0	53.3*
Mild	43.1	28.3	45.6	36.7*
Moderate	37.4	-	32.6	10*
Pronounced	7.2	-	8.8	-
The average body temperature,°C	37.6±0.9	37.4±1.1	37.5±0.9	37.1±0.4

Note: * - the likelihood of difference between the indicators after chemo prophylaxis in the main and control groups ($p<0.05$).

Table 3

Integrative indices of endogenous intoxication in the groups studied in the dynamics of chemoprophylaxis under various schemes (M±m)

Index	BFE (n = 20)	Group 1 (n=144)		Group 2 (n=106)	
		prior to the treatment	after the treatment	prior to the treatment	after the treatment
LII (RVU)	1.3±0.5	1.6±0.05	1.5±0.05	1.55±0.07	1.8±0.07*#
HII (RVU)	1.9±0.46	2.1±0.06	2.3 ±0.07	2.13±0.07	2.99±0.07*#
ISWBC (RVU)	1.8±0.05	2.1±0.06	2.1±0.05	1.95±0.05	2.83±0.05*#
Ilym (RVU)	0.6±0.76	0.55±0.06	0.43±0.05*#	0.46±0.06	0.38±0.05*#

Notes:

1. # index is significantly different from that before treatment ($p<0.05$);
2. # index is significantly different from that in group 1 ($p<0.05$).

tients in group 2 ($p> 0.05$) respectively. The average body temperature of patients was 37.4±1.1 in group 1°C compared to 37.1±0.4 in group 2. It was found that, almost in a similar way, there were no signs of IS (56.7% and 63.3%, respectively, ($p>0.05$)) in the majority of cases both in group 1 and in group 2.

Thus, it was found that the groups of children assigned to chemoprophylaxis were essentially equivalent on clinical signs of IS severity at the beginning of treatment.

However the follow-up chemopreventive treatment showed that a group of children, who received isoniazid in syrup, had a much better efficacy on the main clinical sings of intoxication syndrome.

Thus, it was found that the severe or moderate IS was observed in group 1 after 3 months of chemoprophylaxis, but the moderate IS was remained in 10% of children in the second group ($p>0.05$). In the 1st group the IS was absent in 71.7% of cases at the end of chemoprophylaxis, however, in children receiving isoniazid in tablet form, IS was frequent by 18.4% more, which indicates the lack of effect on the processes of overcoming tuberculosis infection in the body.

Consequently, a group of children who received isoniazid in syrup, had a better efficacy related to the complete disappearance of mild and moderate sings of intoxication in contrast to patients in group 2, where the parameter was equal to 3.4%.

An important part of control of effectiveness of chemoprophylaxis at presence of clinical signs of intoxication in the children at risk examined is to define the syndrome of endogenous intoxication (EI). Endogenous intoxication is poisoning of organism with by-products and waste products of metabolism, resulting from their exceeding accumulation due to either the increased catabolism or the blockade of detoxification systems of the body, in particular, the liver, with subsequent development of system damage. An indirect measure of severity of general condition of patients with various pathological processes is the assessment of the severity of endogenous intoxication [1].

Development of EI syndrome is an essential part of the pathogenesis of tuberculosis [1]. Use of modern computer technology allows us to facilitate significantly the calculations of integrative indices of intoxication, which are the objective criteria of severity of the disease and efficacy of treatment.

After treatment both in the main and control groups, the number of eosinophils and leukocytes in the peripheral blood was significantly decreased, ESR and endogenous intoxication indices were normalized (*Table 3*).

Analysis of LII shows that it is significantly lower (by 1.2 times ($p <0.05$)) in group 1 compared to group 2, but it was stated a slight increase in this index in group 1 from the beginning of treatment (by 1.1 times, $p> 0.05$). It was found that the HII after IF is significantly higher in group 2 compared to group 1 (by 1.3 times ($p<0.05$)), and there is an increase in this index by 1.4 times compared to that prior to the treatment ($p<0.05$). It is evidenced that ISWBC is higher in group 2 compared to the corresponding index in group 1 (by 1.3 times ($p<0.05$)). Lymphocytic index did not differ significantly in both groups.

Thus, according to the results of complex examination under the protocol, the study has confirmed significantly higher efficiency of isoniazid in the form of syrup in use in the programs of chemoprophylaxis for detoxification processes as intergroup values of the parameters were significantly different ($p <0.05$) according to the analysis of EI.

The data show that the bacteriostatic and bactericidal action of antimycobacterial drugs depends on the form of administration, the syrup has a better absorbability - the higher concentration in the blood is, the longer it is maintained at high levels and the higher its bactericidal action is, that explains the high

Table 4

The dynamics of biochemical parameters of blood in the groups studied in the treatment under various schemes

Biochemical parameter	Groups of patients (n=30)	Prior to treatment	After the treatment
Total protein	Group 1	72.1±0.59	64.8±0.41
	Group 2	72.4±0.81	71.7±0.67*
Bilirubin, μmol/l	Group 1	15.1±0.46	16.8±0.48
	Group 2	14.9±0.44	20.3±0.91 #
AST mmol/(h·l)	Group 1	0.51±0.015	0.57±0.013
	Group 2	0.49±0.011	0.78±0.016 #
ALT mmol/(h·l)	Group 1	0.48±0.014	0.51±0.019
	Group 2	0.45±0.012	0.57±0.018
Urea, mmol/l	Group 1	5.2±0.22	5.2±0.11
	Group 2	5.1±0.18	5.4±0.15
Creatinine, (μmol/l)	Group 1	83.5±0.85	91.8±1.23
	Group 2	81.4±0.53	89.1±1.02
Thymol test, (unints)	Group 1	3.45±0.22	4.31±0.32
	Group 2	3.7±0.29	5.10±0.21*#
AST/ALT ratio	Group 1	1.06±0.011	1.12±0.15*#
	Group 2	1.09±0.21	1.37±0.22

Notes:

1. # Index is significantly different from that before treatment ($p<0.05$);
2. # Index is significantly different from that in group 1 ($p<0.05$).

efficiency of administration in the form of syrup, that is consistent with other studies [5,8,10].

According to clinical and biochemical studies, both drugs have no any pronounced negative renal or hepatic effects.

After completion of chemoprophylaxis improvements in the general condition and the positive dynamics of the IS were observed in the overwhelming majority of patients. However, according to our study results a trend towards deterioration of certain biochemical parameters of blood was noted, in particular in the group 2, when in some cases there was a tendency to an improbable increase in bilirubin level, ALT and AST parameters, indicating a toxic effect of chemotherapy in tablet form on metabolic processes in the liver (Table 4).

As shown in table 4, lower levels of total protein was reported in 1 group - by 9.6% than in patients in 2 group ($p<0.05$). Also significantly higher levels of bilirubin - by 17.2 %, ALT (alanine transaminase) - by 19 %, AST (aspartate transaminase) - by 22.4 % and thymol test - by 15.5 % were reported in 2 group compared with 1 group. ($p <0.05$), evidencing that there are preconditions for the development of toxic hepatitis when using isoniazid in tablet form. It is well established that in children who received isoniazid tablets changes in blood chemistry were much more pronounced and increased at the completion of the course of chemoprophylaxis.

Cytolytic syndrome is one of the main, which characterizes the effects of intoxication in the development of tuberculosis infection as well as hepatotoxic effects of isoniazid on the liver. After the analysis it was found that the cytolytic syndrome is observed by 14.2% more frequently in patients treated with isoniazid in tablet form. Also significantly higher levels of bilirubin - by 17.2 %, ALT (alanine transaminase) - by 19 %, AST (aspartate transaminase) - by 22.4 % and thymol test - by 15.5 % were reported in 2 group compared with 1 group. ($p<0.05$), that favours the administration of isoniazid in the form of a syrup. The De Ritis Ratio, i.e. the ratio of AST to ALT also allows us to determine the effects of isoniazid on the functional state of the liver. According to the results obtained the ratio was 1.22 times significantly higher in patients in group 2 than in the control group ($p <0.05$) at the end of the course of chemoprophylaxis.

After 6 months of chemoprophylaxis during an ultrasound examination of the hepatobiliary system the following changes were observed in both groups: slight increase in the maximum oblique diameter of the right liver lobe in 80.0% of patients by (0.7 ± 0.71) mm and was (151 ± 1.21) cm ($p <0.05$), the length of the left lobe in 73.3% of patients - by (0.82 ± 0.12) cm and was (112 ± 2.7) cm ($p <0.05$); signs of diffuse lesions of liver parenchyma structure due to the small echoes of different density, decrease in sound conductivity and increase in the liver parenchymal echogenicity in 68.3% of the children examined with significant trend of most of the changes observed in group 2. Changes in biochemical tests

and pathological signs at ultrasonic research of the digestive system indicate the presence of hepatotoxic, cholestatic or mixed side effects of antimycobacterial drugs which, in particular, are inherent in isoniazid. However, the changes observed did not exceed the age norms.

Consequently, "Isoniazid" received in the form of syrup, was well tolerated by most patients and gave a positive clinical effect. Tolerability of treatment was defined as good in 83.3% of patients in the control group and 98.7% of those in the main group ($p>0.05$); as satisfactory - in 15.1% of children in the control group and 1.3% of children in the main group ($p<0.05$); unsatisfactory (nausea) - 1.6% of children in the control group. No unsatisfactory tolerance was observed in the main group. No potential complications and significant side reactions in children in the main group were reported, which indicates the low toxicity of the drug in the form of syrup.

Conclusions. It was found that the group of children who received isoniazid in syrup, had a better efficacy related to the complete disappearance of mild and moderate symptoms of intoxication in contrast to patients in group 2, where the parameter was equal to 3.4%. The De Ritis Ratio was 1.22 times significantly higher in patients in group 2 than in the control group ($p <0.05$) at the end of the course of chemoprophylaxis.

The results of complex clinical, laboratory, biochemical and instrumental studies allow us to recommend "Isoniazid" syrup 100 mg / 5 ml as highly effective drug for the prevention of tuberculosis in children. The drug can be recommended for chemoprophylaxis of tuberculosis and treatment of BCG complications.

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