Every year about 9 million new TB cases are detected in the world. Nearly 1 million cases (11%) falls on children under the age of 15 years.

Of these, 75% are detected in 22 countries with a high tuberculosis prevalence, which is approximately 80% of TB cases in children detected throughout the world. In general, in various countries children constitute from 3 to 25% or more cases of the total number of persons with tuberculosis [5].

The basic method of complex treatment of tuberculosis patients is etiologic (antimycobacterial) therapy. One of the most effective drug is isoniazid, it is used in complex combination treatment as well as during chemoprophylaxis [3, 4].

Preventive treatment as a way to prevent TB is used around the world. Chemoprophylaxis schemes are different mainly by treatment duration ranged from 3 to 12 months in different countries. Isoniazid (and its analogues) is the only drug that is used alone without combination with other anti-TB drugs [4, 5].

In Ukraine, the children at risk who are under the supervision of the children's phthisiatician and undergo the appropriate examination and if necessary preventive treatment, constitute every year about 200 thousand of people. Taking into the consideration the duration of treatment and age characteristics of the child, it is important to use a convenient form of the drug [2].

For patients treatment isoniazid of Ukrainian manufacturers is used in most of cases: tablets, solution for parenteral use and isoniazid in syrup. The last one is increasingly used in pediatric practice.

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 required for the mycobacterial cell wall. Drug has high bacteriostatic and bactericidal activity against Mycobacterium tuberculosis (MBT) - their growth is delayed in isoniazid concentration 0.03 mg/ml. M. tuberculosis and M. Bovis are highly sensitive to isoniazid, while it has low effectiveness against the causative agents of other infectious diseases.

The drug is well absorbed from GI tract, easily penetrates the blood-brain barrier, enter the spinal fluid, pleural effusion fluid, ascitic fluid, sputum, saliva, lungs, skin, cheesy mass. Time to reach maximum concentration levels (Tmax) in a blood is 1-4 hours.

Binding to plasma proteins is 10%. Volume of distribution is 0,56-0,76 l/kg. Tuberculostatic concentration after single dose administration persists for 6-24 hours. Drug crosses the placenta and is excreted in breast milk.

Isoniazid is metabolized in the liver by acetylation. Metabolism rate is genetically determined and depends on the level of activity of N-acetyltransferase. Depending on the rate of acetylation patients are divided into "fast" and "slow" inactivators. In "fast" inactivators isoniazid half-life is 0,5-1,6 hours, and the amount of unchanged substance excreted by the kidneys is less than 10% per day. In the "slow" inactivators these indicators are 2-5 hours and more than 10% per day respectively. In newborns the half-life is 7,8-19,8 hours, in children aged 1,5-15 years - 2,3-4,9 hours. Drug is excreted by the kidneys mainly as inactive metabolites: within 24 hours 75-95% of the administered dose is excreted with urine, a small amount excreted in feces [4]. Isoniazid is the most effective in acute processes; it is used for the treatment of active tuberculosis of different localization in adults and children as the main drug.

In therapeutic doses isoniazid is well tolerated by patients. In rare cases, adverse reactions can be observed: dizziness, nausea, vomiting, gastritis, sometimes - increased fatigue, headache, insomnia, paresthesia; in children - excitement and in some cases abnormal liver function, skin rash, itching, eosinophilia, fever, retrosternal pain, and in rare cases gynecomastia, dysmenorrhea may develop due to stimulation of the adrenal glands.

Isoniazid is contraindicated in case of hypersensitivity. Drug should be prescribed cautiously to patients with epilepsy and other diseases with a tendency to seizures, in the case of history of polyneuritis, impaired renal or/and liver function and atherosclerosis. Drug dosage above 10 mg/kg is contraindicated in pregnancy, lung-heart failure of stage III, hypertension of stage II-III, ischemic heart disease, widespread atherosclerosis, diseases of the nervous system, asthma, psoriasis, eczema in the acute phase, chronic renal failure, acute phase of hepatitis, liver cirrhosis, hypothyroidism.

Comparative study of efficacy and safety of syrup of isoniazid was conducted in 60 children with pulmonary tuberculosis aged 6 to 18 years in accordance with the requirements for such studies of State Pharmacological Center of MoH of Ukraine. The study was carried out as an open comparison, parallel clinical trial. Isoniazid syrup 100 mg/5 ml was administered for 30 children of the basic arm. Control arm consisting of 30 children with pulmonary tuberculosis received Isoniazid, syrup 50 mg/5 ml of the "Pharmascience Inc." (Canada) as a part of complex treatment. Patients of a basic arm took isoniazid syrup at a dose of 10 mg/kg (or 0.5 ml/kg) once per day after breakfast for 2 months. Patients of the control arm received the reference drug isoniazid, syrup at a dose of 10 mg/kg (or 1.0 ml/kg) once per day after breakfast daily for 2 months.

Syrup of isoniazid was administered as a part of complex treatment along with other antimycobacterial drugs - rifampicin and pyrazinamide.

Complex therapy also included vitamin B6 (pyridoxine hydrochloride), glutamic acid, vitamin B1 (thiamine chloride), adenosine triphosphate sodium salt (ATP), hepatoprotective agent on the basis of silymarin in the appropriate dosages. Following drugs were prohibited to administer during the study:
hepato-and neurotoxic drugs, antibiotics, sulfonamides, indirect coagulants, benzodiazepines, phenytoin, carbamazepine, theophylline, MAO inhibitors.

All patients were divided at random into 2 arms: basic arm (30 persons) and control arm (30 people), identical in gender, age, place of residence, duration of disease and degree of expression of major clinical signs.

Before including the patient in the trial collected and recorded in case report forms data were evaluated: demographic (gender, age), physical (height, weight), history (of life and disease), radiological (X-Ray of the chest, CT), a clinical examination (examination of the patient, palpation, percussion, auscultation), blood pressure (BP), heart rate (HR), body temperature (°F), laboratory data (complete blood count, urinalysis, blood chemistry), microbiological (bacterioscopy, sputum or bronchial lavage culture). Patients and their parents (guardians) signed informed consent to participate in the research and then adequately cooperated with doctors throughout the period of treatment and examination.

Observations and examinations of patients were performed in stages: screening (the first 2-3 days after hospitalization) and during the entire treatment period (60 days): 1st-3d, 15th, 30th, 45th, 60th days. Researches and recordings were carried out in accordance with the developed scheme.

All survey data were written in the case history and case report form. Children with verified diagnosis of lung tuberculosis who met the criteria for inclusion/exclusion to the the study mentioned above were included in the clinical trial.

According to the trial protocol, assessment of efficacy was carried out by the following criteria:

- main criteria - the dynamics of clinical manifestations of tuberculosis (subjective symptoms and complaints of patients, objective data, laboratory tests), the dynamics of X-ray data;
- secondary criteria - the dynamics of contagiousness according to microbiological examination of sputum or bronchial lavage water (in MBT-positive patients).

Drug effectiveness was evaluated using the above criteria for a common effectiveness scale: an effective drug - an ineffective drug.

Signs were scored according to their degree: 0 - no symptoms, 1 - weak symptom or presence of sign (in the case of gradation "yes-no"), 2 - moderate degree of expression, 3 - significant severity of symptom.

The drug tolerance was evaluated on the basis of subjective complaints of the patient and objective data obtained by the investigator. Dynamics of laboratory parameters as well as the incidence and nature of adverse reactions were considered.

Particular attention was paid to the following signs: nausea, vomiting, GI disorders, pain in the stomach, liver dysfunction, irritability, excitement, dizziness, headache, euphoria, sleep disturbances, paresthesia, palpitation, retrosternal pain, allergic reactions (eosinophilia, itching and rash, fever), peripheral neuritis, psychosis, gynecomastia, menorrhagia, hepatitis. The drug tolerance was assessed using objective data in accordance with the Scale of assessment of drug tolerance (tolerance - good, satisfactory, unsatisfactory).

Only patients completed a full course of treatment were included in the efficiency analysis. Patients with any violation of trial protocol (inclusion/exclusion criteria, plan of treatment etc.) were excluded from effectiveness and tolerability analysis.

Statistical analysis was carried out by parametric methods using Student's t-test if test results followed the normal distribution. In other cases non-parametric methods and Wilcoxon test were used [5].

A noticeable improvement in clinical signs dynamics was detected on the 30th day of treatment with isoniazid in combination with other drugs. On the 60th day of treatment condition has improved considerably in 87.6% of patients.

Most of children were in infiltration phase of disease, a third part of all children - in the phase of necrosis, and a quarter of patients - in the phase of seeding. There were no significant differences between groups for these parameters in the dynamics of treatment. Under the influence of treatment on the 60th day resorption of most of focuses of contamination and reducing the size of destruction in the lungs were noted in the (70.0 ± 8.3)% of patients of the basic arm and in (63.3 ± 7.9)% of children of a control arm. Rate of healing of necrotic cavities and resorption of focuses of contamination was 6.7% in the basic arm and 3.3% in control arm, P> 0,05. Significant positive dynamics of X-ray at the end of the 2nd month (substantial resolution of infiltrates in the lungs) was noted in (90,0 ± 9,5)% of children in basic arm and in (86,7 ± 9,3)% of control arm. In other words, the findings showed the same effectiveness of study and reference drugs.

After treatment significant decrease of the leukocytes and eosinophils count in the peripheral blood, ESR, increased lymphocytes count were observed in both basic and the control arms.

According to clinical and biochemical studies, both drugs had no negative effect on the kidneys and liver.

Microbial examination of sputum was carried out in approved terms. Thus, before treatment mycobacterium culture was positive in 2 (6.7%) patients of basic arm and 1 (3.3%) patient of control arm. In the control examination there was no patients with positive MTB culture.

The studied drug was well tolerated and gave a positive clinical effect in the majority of patients. Tolerability of treatment was defined as good in 25 (83.3%) patients in the control arm and in 29 (96.7%) of the basic arm (P> 0,05); as satisfactory - in 4 (13.3%) children of the control arm and in 1 (3.3%) children of the basic arm (patient N 14), P> 0,05; unsatisfactory (nausea) - in 1 (3.3%) child of the control arm. There were no cases of drug intolerance in the basic arm.

Possible complications and severe adverse reactions in patients of basic and control arms were not observed, indicating low toxicity of medicinal products.

data of the trial allow to recommend the use of Ukrainian drug isoniazid, syrup 100 mg/5 ml as a highly effective medications in treatment of children with TB.

The drug can be recommended for chemoprophylaxis of tuberculosis and treatment of complications of BCG immunization.

**LITERATURE**


