Comparative Characteristics of Dosage Forms of Benzatin Benzylpenicillin in Practical Use in the Prevention of Rheumatic Fever

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ABSTRACT

in the course of comparative practical characteristics, the clinical profile of two dosage forms benzatin benzylpenicillin at a dose of 2.4 million units and bicillin-5 was evaluated. The study included 60 people (33 women and 27 men aged 16-45 years) with confirmed chronic rheumatic heart disease (CRD) without signs of circulatory insufficiency. The evaluation of the effectiveness of benzylpenicillin was evaluated by EchoCG control and laboratory data indicating the activity of the process 6 and 12 months after regular intramuscular injection of one of the drugs once every 3 weeks. The administration of extenbenzatin at a dose of 2.4 million units (32 people) prevented the development of recurrent rheumatic fever, which was ensured by a likely stable concentration of benzatin benzylpenicillin for a 3-week period. With the injection of bicillin-5 1.5 million units (28 people), relapses of rheumocarditis were observed in 58% of cases, due to a decrease in the concentration of benzylpenicillin by 3 weeks. Thus, long-term preventive treatment with benzatin benzylpenicillin at a dose of 2.4 million units shows high effectiveness in preventing repeated attacks of rheumatic fever.

Rheumatic fever is a disease that often occurs as a complication of tonsillitis (sore throat) or pharyngitis caused by a bacterium – group A streptococcus, in which the heart, joints, and nervous system are affected. Involvement of the heart is irreversible, damage to the joints and nervous system is reversible. It is noteworthy that heart damage may be asymptomatic for several years. Repeated RL attacks increase the degree of destruction of the heart valves and lead to the formation of acquired rheumatic heart disease (RPS) or chronic rheumatic heart disease (CRHD).

Currently, the drug bicillin-5 (a mixture of 1.2 million units of benzathine benzylpenicillin and 300 thousand units of novocaine benzylpenicillin salt), according to Russian rheumatologists and cardiologists, is considered as not meeting the pharmacokinetic requirements for preventive drugs, and is not acceptable for carrying out a full-fledged secondary prevention of ARL [16]. The purpose of this work is to evaluate the practical effectiveness of two dosage forms benzatin benzylpenicillin and bicillin-5 during an open randomized comparative trial.

Material and methods of research. At the first stage of the work, in order to study the informative value of evaluating the effectiveness of prevention with benzatin benzylpenicillin, an express method of diagnosing group A streptococcus antigen (CAA) from the pharynx was performed in 50 adult patients (33 women and 27 men aged 16-45 years) with a history of diagnosed CRHD. Along with the express method, bacteriological seeding of the contents of the smear from the pharynx for the presence of microflora and its sensitivity to antibiotics was performed. The diagnosis of CRHD and rheumatic fever was established on the basis of WHO recommendations on the Jones diagnostic criteria as modified by the American Heart Association (AHA, 1999), the Association of Rheumatologists of Russia (ARR, 2003) and the World Heart Federation (2008). In accordance with the purpose of the work, 2 groups of examined persons who underwent outpatient examination and inpatient treatment were formed by randomization. The first group (32 people) received benzatin benzylpenicillin at a dose of 2.4 million units (group A), the second (28 people) - bicillin-5 at a dose of 1.5 million units (group B). All drugs were administered deeply intramuscularly once every 3 weeks for a long time for 12 months.

At the II stage of the work, a clinical and functional assessment of the course of CRHD (the presence of repeated attacks of rheumatic fever) was carried out in patients receiving benzatin benzylpenicillin prophylaxis, with an analysis of risk factors predisposing to the development of the disease. Informed consent was obtained from all persons included in the test before starting work. The exclusion criteria were: 1) the use of antibiotics during the study and for 1.5 months before it begins; 2) taking medications that affect hemodynamics (cardiac glycosides, diuretics, peripheral vasodilators); 3) intolerance to betalactam antibiotics, documented in doubtful cases; 4) renal and/ or hepatic insufficiency; e) pregnancy and lactation. In addition, patients with a history of tonsillectomy, the presence of concomitant diseases affecting the state of the heart (congenital heart defects, myocarditis, cardiomyopathy), the presence of chronic heart failure, cerebral circulatory disorders, hypertension, diabetes mellitus were excluded from the study. To carry out this work, a unified registration card was developed, which included general information about the patient, medical history, results of a general clinical examination, FC CH, heart rate (HR), laboratory data including antistreptolysin-O titers (ASL-O), results of bacteriological seeding from the throat and an express method for diagnosing the antigen of CAA, ECG data in 12 standard leads and EchoCG with Doppler examination.

Indicators of the inflammatory process in our study were ESR, CRP, acute phase proteins with an increase in the concentration of gamma globulins and other globulin fractions. Using the enzyme immunoassay (ELISA) reaction, an increase in immunoglobulin (Ig) of classes A, M, and G. The determination of group A streptococcus antigen was carried out by an express diagnostic method of antigen agglutination reaction using rapid tests from a smear taken from the surface of the tonsils or the posterior wall of the pharynx, according to the recommendations of the American Society of Infectious Diseases

For bacteriological studies, swab samples were taken from the pharynx, which were studied with the identification of bacteria in the bacteriological laboratory.

Echocardiographic and dopplerographic studies were carried out on Vivid-q and PHILIPS Ultrasound MOD iE33 devices with a Doppler prefix in the standard position of the subject on his back. To assess the echostructures of the heart and valvular apparatus, M and B scans were used.

The following indicators were analyzed:
- PDR LP - antero-posterior size of the left atrium, see
- CDR LV - end-diastolic size of the left ventricle, see
- LV CSR - of course-systolic size of the left ventricle, see
- Pancreas - right ventricle, see
- PSLJ - thickness of the anterior wall of the right ventricle, see
- ZSLJ - thickness of the posterior wall of the left ventricle, see
- MZHP – thickness of the interventricular septum, see
- LV – ejection fraction of the left ventricle, %.
- Systolic FRET – systolic pressure in the pulmonary artery, mmHg. art.
- Average FRET – average pressure in the pulmonary artery, mmHg. art.

The presence of thickening of the flaps of the aortic, mitral, tricuspid valves was assessed. The criterion for thickening of the valves of the heart valves was considered to be the thickness of the valves > 5mm. The sign of pericarditis was an echonegative space > 5mm in the systole. The sealing of valve flaps and pericardial leaves was evaluated by the intensity of ultrasonic reflection. The use of Doppler technique made it possible to assess the state of intracardiac blood flow, identify mitral or aortic regurgitation as an early sign of valvulitis, and assess its volume. The II standard ECG lead was recorded synchronously.

Methods of statistical processing. Statistical processing of the results of the study was carried out using methods of variational statistics using standard statistical programs EXCEL 5.0, STATISTICA 6.0. Statistical processing of the data obtained included the calculation of the arithmetic mean M and standard deviation (δ). The reliability of the differences between the groups was determined using the Student's criteria, the χ-square, the odds ratio (OR) and the Z-criterion. The differences were considered statistically significant with an uncertainty probability of less than 5% ($p<0.05$).

The results of the study and their discussion. Comparative analysis of rapid diagnostics for group A streptococcus antigen and bacterial inoculation of a pharyngeal smear in the examined adults.

In order to study the informativeness of the express method of diagnosing group A streptococcus antigen in 100 patients with CRHD, along with the express method, bacteriological seeding of the contents of a smear from the pharynx was performed, which we selected as a reference test. Of the 60 patients examined by us, 15 patients (34.0%) by express

method and 27 patients (42.0%) with bacterial seeding revealed the presence of CAA. So, analyzing the data obtained in patients with CRHD, we can note a similar high incidence of CAA, obtained by both express method and bacterial seeding.

The conducted statistical analysis showed that in comparison with the reference test – bacterial seeding - the express method used by us has high specificity (54/58 or 93.1%), and sufficient sensitivity (30/42 or 71.4%)

Risk factors for the development of acute rheumatic fever. Next, we studied the influence of various factors on the risk of developing ARL, which was estimated by the odds ratio (OR) with the calculation of a 95% confidence interval (CI), i.e., by the ratio of events (i.e., the presence/absence of a risk factor) in patients with CRHD.

As follows from the data presented in Table 3, the most significant increase in the risk of developing RL was noted in the presence of a patient with a syndrome of connective tissue dysplasia of the heart (DSTS). Thus, in the presence of DSTS syndrome, the risk of developing ARL increased by more than 8 times (OR-8.2; 95% CI 4.1-60.4; p<0.005)

A significant increase in the risk of developing RL was noted in patients with tonsillopharyngitis. According to the results of our study, the presence of tonsillopharyngitis was associated with an almost 6-fold increase in the risk of developing RL (OR - 5.8; 95% CI 3.26-10.33; p<0.05).

Attention is drawn to the presence of gender differences in the predisposition to the development of RL. Thus, according to our data, women are more than 1.5 times more likely to develop RL than men (OR -1.55; 95% CI 1.05-2.47; p<0.05).

Clinical and functional features of the course of CRHD against the background of benzatin benzylpenicillin prophylaxis. After 6-12 months of the control examination, 16 (58.3%) patients from group B (n-28) and 4 (13.4%) patients from group A (n-32) had clinical symptoms of carditis with Echo-KG signs of valvulitis. Mitral valvulitis was found in 9 (25.7%) of the total number of patients with repeated RL, 5 (25.7%) had valvulitis of the aortic valve (Table 4). 12 (46.2%) patients had valvulitis of the mitral and aortic valves simultaneously. At the same time, mitral valve valvulitis was detected in 2 (12.6%) patients from group A and in 7 (25.0%) patients from group B. Aortic valve valvulitis was more often registered in group B (28.6%, versus 14.2% in group A, RD-0.14; 95% CI 0.01-0.29; p<0.001)

Echocardiographically, the RL pattern was characterized by the presence of an increase in marginal seals (thickenings) of valve flaps with looseness of contours and an increase in mitral and/or aortic regurgitation from a minimum and/or I-II degree to a clear I and/or II-III degree. In addition, there was an increase in LV CDR, LV CSR, and LP heart rate. Heart damage in RL in the examined groups was characterized not only by the picture of endocarditis (valvulitis), but also by the phenomena of myocarditis. On the ECG, transient ventricular extrasystoles were observed in 7 patients with RL: in 6, the Laun I gradation and in 4, the Laun II gradation. In addition, blockade of the anterior branch of the left leg of the Gis bundle was detected in 12 patients and atrioventricular blockade of I-II degree (Mobitz I-II) was detected in 4 patients. Pronounced polyarthritic syndrome with arthritis phenomena in large and medium joints was registered in 2 patients (5.7% of cases) from group B, manifested by severe pain and impaired joint function. At the same time, it should be noted that joint syndrome in the form of polyarthralgia is more common (Table. 5) was observed with RL in group B (46.4% vs. 14.2%; RD – 0.30; 0.16-0.45, p<0.0001).

Acute-phase blood reactants (ESR, CRP) included in the "small criteria" of RL did not

always correspond to the clinic of cardiitis. Thus, 4 patients (17.1% of cases) were characterized by a latent course of the disease, when all acute-phase indicators were within normal values, while RL was diagnosed according to EchoCG, ECG criteria and the presence of polyarthralgia. Minimal activity of the rheumatic process was observed in 16 patients (35.7% of cases). At the same time, clinical symptoms were poorly expressed, moderate or mild signs of rheumocarditis, polyarthralgia were observed. In these cases, the presence of activity of the rheumatic process was verified taking into account any two "small criteria" of RF. In 8 patients (15.7% of cases), RL proceeded with moderate activity with accelerated ESR, insignificant neutrophilic leukocytosis, and the absence of a pronounced exudative component of inflammation. At the maximum degree of activity in 3 patients (9.4% of cases), the general and local manifestations of the disease were bright with the presence of fever, the predominance of the exudative component of inflammation in the affected organs (arthritis, diffuse myocarditis, pancarditis).

In addition, with repeated (after 6-12 months) rapid diagnosis of the CAA antigen from the pharynx in patients receiving benzatin benzylpenicillin prophylaxis, only 3 patients from group B had a positive result. But bacterial sowing, at the same time, did not give them growth. Conclusion: Thus, in patients with CRHD receiving regular secondary prophylaxis with benzatin benzylpenicillin, frequent clinical manifestations of relapse of rheumocarditis were noted in the group of patients receiving Bicillin-5. Moreover, it was found that the use of penicillin benzatin in the form of bicillin-5 does not provide adequate anti-streptococcal concentration of penicillin in the long term and, therefore, is not acceptable for full-fledged prevention of RL. In this regard, I would like to note the importance of conducting proper primary and secondary preventive work at the primary health care level. In addition, it is necessary to eliminate RL risk factors through the rehabilitation of nasopharyngeal and oropharyngeal infections, such as carious teeth, sinusitis (sinusitis, frontitis, ethmoiditis). Secondary prevention of RL involves the regular administration of prolonged-acting penicillin benzatinbenzylpenicillin, administered at a dose of 2.4 million units intramuscularly 1 time every 3 weeks. I would like to note that long-term preventive treatment with extenbenzatin in patients who have undergone RL has shown high effectiveness in preventing the progression of the disease and its repeated attacks.

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