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EFFICACY OF LONG-ACTING PENICILLINS IN COMBINATION WITH DOXYCYCLINE IN THE TREATMENT OF EARLY STAGE SYPHILIS

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Introduction

For more than three decades since the discovery of penicillin, it remains a unique drug. Penicillin and its derivatives turned out to be the most effective means of specific therapy for syphilis. They still don't have a decent alternative. These antibiotics penetrate well into the lymph and lymph nodes, which are the reservoir of *T. pallidum* [1]. The use of sodium and potassium salts of benzylpenicillin is effective, but requires administration of the drug every 3-4 hours, which is possible only in hospital conditions. Durant penicillin preparations - bicillins allow reducing the number of injections to 1-2 per week, but they do not always provide a stable concentration of penicillin in the tissues. In recent years, data on frequent cases of clinical and serological relapses, seroresistance, as well as the development of neurosyphilis and other late forms in patients treated with long-acting penicillins began to accumulate [3, 7]. Obviously, the euphoria caused by the first successful experience of using Durant penicillins, when syphilis was cured "with one injection" has already passed. This especially applies to weakened patients with concomitant pathology, alcohol and drug intoxication, HIV-infected patients and those living in environmentally disadvantaged areas. Therefore, there is a need to develop new methods of specific therapy of syphilitic infection, taking into account the modern features of the epidemiology, clinic and pathogenesis of syphilis.

Reserve antibiotics can be used in the treatment of early forms of syphilis: tetracyclines, macrolides, cephalosporins [5]. There is very poor data on doxycycline, which has high activity against the causative agent of syphilis and is included as a backup drug in existing treatment methods [6]. These data allow us to assume the effectiveness of the drug, but they do not allow us to determine the optimal dose and duration of treatment, as well as the possible effect when it is combined with penicillin drugs [4].

The aim of our study was to develop a new method of treating patients with early forms of syphilis with benzathine benzylpenicillin in combination with doxycycline. To conduct a comparative analysis of the immediate and distant results of the treatment of syphilis patients using the developed methodology.

Materials and methods. A total of 537 patients with active early syphilis (term of infection up to 1 year) were treated and observed, who made up three studied groups (main, control and comparison group)

The main group (293 patients) was treated with benzathine benzylpenicillin simultaneously with doxycycline. The control group (78 patients) received only benzathine benzylpenicillin. And the comparison group (166 patients) received the sodium salt of benzylpenicillin. Course doses were determined by the form of syphilis.

All patients underwent a clinical and laboratory examination (general tests of blood, urine, feces), as well as serological reactions for syphilis and HIV (ELISA). Serological examination at the time of diagnosis included KSR, RIF-200, RIF-abs, RIT. For clinical and serological control of treatment results, the dynamics of the disappearance of syphilides and the rate of negation of the standard complex of serological reactions - KSR were used. Since the rate of KSR negation is determined not only by the effectiveness of treatment, but depends on the duration of infection, the comparison of the dynamics of negation was carried out only within the subgroup of patients with the same form of syphilis (that is, primary syphilis was compared with primary, secondary fresh with secondary fresh, and secondary recurrent with secondary recurrent).

Statistical processing of the obtained qualitative and quantitative indicators was carried out using a standard package of application programs, a relational database was also created in the Microsoft Access program, which included clinical and laboratory data on all studied patients. Quantitative data and logit values were imported into Microsoft Excel, where descriptive statistics were calculated for each sample being compared using built-in statistical functions: mean, standard error, mode, median, standard deviation, skewness variance, and kurtosis. Comparison of group means was performed using Z-test and t-test. Analysis of variance (F-test) and regression analysis were used to compare the dynamics of the disappearance of clinical manifestations and the rate of KSR negation. The level of reliability was accepted as 95%. For the quantitative analysis of the dynamics of the negation of serological reactions, the function "Slope of the linear regression line" was evaluated [1, 6].

Analysis of the immediate results of treatment of syphilis patients with three methods - benzathine benzylpenicillin and doxycycline, only benzathine benzylpenicillin and sodium salt of benzylpenicillin showed their effectiveness. This is evidenced by the dynamics of resolution of active manifestations of the disease on the skin and mucous membranes.

Syphilides disappeared quite quickly, and the time of disappearance was comparable to the data of other researchers who studied the effectiveness of penicillin drugs in syphilis [1]. In a comparative analysis of three treatment methods, it was found that when treated with benzathine benzylpenicillin in combination with doxycycline, individual active manifestations of syphilis disappeared faster on average than when

treated with benzathine benzylpenicillin alone. Erosive chancre - for 2.6 days; ulcerative chancre - for 3.1 days; roseola - for 1.5 days; wide condylomas - for 3.2 days; papules in the oral cavity - for 1.6 days. The terms of resolution of papules on the genitals and papules on the palms and soles were almost the same in the subgroups compared. p align="justify"> A significant acceleration of resolution in the main subgroup was found for regional scleradenitis - by 3.8 days ($P=0.004$); wide condylomas - by 3.2 days ($P=0.002$) and syphilitic tonsillitis - by 4.1 days ($P=0.0001$).

In the comparative analysis of the dynamics of resolution of clinical manifestations of early syphilis in the main group and the comparison group that received the sodium salt of benzylpenicillin, no significant differences were found.

The obtained results can be considered as an advantage of the proposed method of treatment of early syphilis. Obviously, when benzathine benzylpenicillin and doxycycline are prescribed, the pathogen is eliminated more quickly, which accelerates the resolution of active manifestations, which are the reaction of tissues to treponemes and their waste products.

It should be noted that the effectiveness of syphilis treatment cannot be conclusively judged only from the dynamics of the disappearance of syphilis. For final conclusions, it is necessary to study remote results, the direct reflection of which is the dynamics of negative serological reactions. The term "dynamics of negation" refers to the rate of decrease in the number of antibodies to *T. pallidum* and the time required for their complete disappearance. The dynamics of the negation of serological reactions can be quantitatively assessed using regression analysis, which allows comparing subgroups of patients who differ only in the method of therapy being administered [2, 4].

The long-term results of treatment were analyzed in all patients based on the dynamics of negative serological reactions during clinical and serological control of treatment results up to 18 months. The dynamics of negative serological reactions in the main group and the comparison group differ. In patients who were treated with benzathine benzylpenicillin in combination with doxycycline, negation occurs faster.

The application of our proposed criteria for evaluating the dynamics of negation using regression analysis made it possible to identify differences that were not detected by the usual comparison of the terms of negation of serological reactions. The analysis of the curve reflecting the cumulative percentage of negativity over time, namely the estimation of the slope of the linear regression line allows for a better analysis of the long-term results of treatment. To characterize the dynamics of negation of serological reactions in the subgroups being compared, the cumulative percentage of negation was used. This is an indicator of the share of patients in the research sample who tested negative by this time or earlier. The graphic representation of the dynamics of negation in the compared subgroups had the character of an accumulation curve. Regression analysis of this curve made it possible to quantitatively assess the dynamics of negation in subgroups and compare them with each other.

In case of primary syphilis in the main group and the control group, the slope of the linear regression line is 5.46 and 6.25, respectively. The regression coefficient for

the compared subgroups with primary syphilis is as follows: - 12.41 in the main group and 38.46 - in the control group.

In the case of secondary fresh syphilis in the main group, negation occurred faster compared to the control group treated only with benzathine penicillin. The slope of the linear regression line is 7.45 and 6.79, respectively.

In the case of secondary recurrent syphilis in the main group, negation also occurred faster compared to the control group. The slope of the linear regression line is 6.19 and 6.09, respectively.

During a comparative analysis of the dynamics of KSR negation in the main group of patients who received benzytinbenzylpenicillin in combination with doxycycline, and the comparison group who received the sodium salt of benzylpenicillin, no significant differences were found (Figs. 1-3). This testifies to the approximately equal effectiveness of both methods during the treatment of early forms of active syphilis.

Thus, in patients who were treated with benzathine benzylpenicillin in combination with doxycycline, the negation of the complex of serological reactions to syphilis occurred faster compared to patients who were treated only with benzathine benzylpenicillin. This testifies to the favorable long-term results of the method being studied and its high effectiveness for medicine treatment of early syphilis. The method is easy to use and can be recommended for outpatient treatment.

Conclusions.

The immediate and distant results of the treatment of patients with active early syphilis with the introduction of 2.4 million units of benzathine benzylpenicillin 1 time (No. 2-4) per week in combination with taking doxycycline internally at a dose of 0.1 g twice a day for 10-20 days (depending on from the time of infection) testify to the high efficiency of these methods and the possibility of their application in outpatient and day hospital settings.

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