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WAYS TO PROMOTE THE EFFICIENCY OF HERPETIC STOMATITIS TREATMENT

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Ключові слова: *вірус простого герпесу, герпетичний стоматит, інозин пранобекс, комплексне лікування, імунологічні показники*

Abstract. Ways to promote the efficiency of herpetic stomatitis treatment. Lutsenko R.V., Moisieieva N.V., Sydorenko A.H., Ostrovska H.Yu., Kapustianska A.A. *The treatment of herpetic stomatitis should be etiotropic, pathogenetic, symptomatic, and local. The research determined the effectiveness of inosine pranobex (1000 mg 4 times a day) in herpetic stomatitis treatment. Addition of inosine pranobex to the pharmacotherapy of herpetic stomatitis reduced hospital stay and duration of treatment. The drug suppresses the synthesis of the virus due to the structure of inosinic acid in the polyribosomes of the cell affected by the virus, and also helps to eliminate the deficiency or dysfunction of immunity that occurred in the case of herpetic stomatitis, it affects the activity of T-cytotoxic lymphocytes and natural killers, enhances the action of neutrophil granulocytes, chemotaxis and phagocytosis of monocytes and macrophages, increases the synthesis of interleukins IL-1 and IL-2, affects the number of Ig G immunoglobulins. Applying inosine pranobex also significantly decreased pain syndrome manifestations from the start of the treatment. It contributed to body temperature normalization 2 days earlier which shortened the treatment period at the in-patient department. Applying inosine pranobex in the combination therapy of herpetic stomatitis has shown a potent clinical efficacy and can be an alternative to acyclic nucleosides in patients with herpetic stomatitis of the oral mucosa.*

Реферат. Шляхи підвищення ефективності лікування герпетичного стоматиту. Луценко Р.В., Моісєєва Н.В., Сидоренко А.Г., Островська Г.Ю., Капустянська А.А. *Лікування герпетичного стоматиту має бути етіотропним, патогенетичним, симптоматичним та місцевим. У роботі визначили ефективність застосування інозин пранобексу (1000 мг 4 рази на добу) у лікуванні герпетичного стоматиту. Додавання інозин пранобексу до фармакотерапії герпетичного стоматиту зменшило терміни перебування в стаціонарі та тривалість лікування. Препарат пригнічує синтез вірусу через будову інозинової кислоти в полірибосомі ураженої вірусом клітини, а також сприяє усуненню дефіциту або дисфункції імунітету, яка виникала при герпетичному стоматиті, впливає на активність Т-цитотоксичних лімфоцитів та натуральних кілерів, підсилює дію нейтрофільних гранулоцитів, хемотаксис та фагоцитоз моноцитів і макрофагів, збільшує синтез інтерлейкінів IL-1та IL-2, впливає на кількість імуноглобулінів Ig G. Також застосовування інозин пранобексу більш виражено зменшувало прояви больового синдрому вже від початку лікування. Це сприяло нормалізації температури на 2 дні раніше, що скоротило терміни лікування в стаціонарі. Цей лікарський засіб проявив клінічну ефективність та долучений до схеми лікування у хворих на герпетичний стоматит слизової оболонки порожнини рота.*

One of the significant problems of modern medical and pharmaceutical science, medical practice is infectious diseases caused by viruses. Despite the achievements of modern science, herpesvirus infection, which remains one of the most common human viral diseases, does not lose its relevance. To date, 8 antigenic serotypes of the herpes virus are known, which cause various human diseases and are quite widespread throughout the globe. Over the last decade, there has been an increase in the specific weight of herpetic lesions in the structure of diseases of oral mucosa (OM) in adults and children worldwide. This is related to the wide spread of the herpes simplex virus (HSV) in various countries of the world, which reaches 90-95%, its persistence in the human body throughout life, often with a

recurrent course and resistance to various treatment measures [8, 12].

A person encounters this virus for the first time at the age of six months to three years, when infection occurs, which in 80% of cases occurs without clinical symptoms [7, 18]. For quite a long time, the virus persists as a latent infection in the epithelial cells of the oral mucosa, or ganglia, and when inflammation is activated, it reaches the site of clinical manifestations via nerve pathways [5, 17, 18].

Many different factors play a provocative role and lead to a decrease in the body's immunological resistance. In particular, the recurrence or exacerbation of somatic pathology, excessive insolation, frequent hypothermia, injury to the mucous membrane, allergic reactions, stress lead to HSV activation in the human body. Among the causative agents of human herpes simplex infection, two main antigenic groups are distinguished, and the most widespread is HSV-1, which more often leads to labial herpes or herpetic stomatitis, keratitis, encephalitis development. Two main ways of transmission are airborne and contact one [12].

Labial herpes and herpetic stomatitis account for up to 40% of the entire structure of OM pathology, and in 20% of cases, herpetic stomatitis with herpetic rashes on the skin is observed. Nevertheless, herpetic stomatitis (HS) remains one of the widespread forms of primary herpes. HS is an acute, highly contagious lesion of the respiratory tract, accompanied by the phenomena of general intoxication, local manifestations of grouped vesicular rashes on the mucous membranes and skin. The severity of HS course depends on many factors and is divided into three degrees of severity: mild, moderate and severe. In addition, there are periods of infection development: incubation, prodromal, period of clinical manifestations, recovery.

First time, symptoms of HSV infection in adults are characterized by symptoms of stomatitis, herpetic tonsillitis or pharyngitis. In children, HS develops rapidly and most often is localized on the red border of lips and facial skin near mouth [9, 16].

Infection and spread of HSV, variety of symptoms of the disease, and difficult pathogenesis make the problem of herpes treatment quite relevant today. Treatment tactics for HS: use of ethiotropic, pathogenetic and symptomatic therapy. Moreover, both local and general methods of treatment are used. Usage of only local treatment is unacceptable, as these methods, even state-of-the-art, do not allow HSV to be completely eliminated from the human body. Therefore, it is necessary, along with the accepted local treatment, to use combined therapy with drugs that inhibit the reproduction of HSV during the exacerbation period and that would contribute to the formation of an appropriate immune response of a human body in the focus of infectious process, blocking the active process of HSV [3, 11, 13].

Acyclic nucleosides, in particular acyclovir, are the most widely used today among antiviral drugs [8, 16]. Acyclovir suppresses the synthesis of viral DNA in the middle of infected cells, and acyclovir triphosphate is involved in the DNA chain of the viral cell, which leads to termination of the synthesis of the viral DNA chain [2, 15]. Representatives of these antiviral agents are penciclovir, valacyclovir, famciclovir, ganciclovir and others, which belong to the same pharmacological group, but have different pharmacokinetic features, different side effects and development of drug resistance.

According to current data, up to 57% of patients with recurrent herpes have resistance to acyclovir, so the search for new means or approaches to the treatment of herpes infection becomes very urgent [15, 16].

Taking into account all the complexities of HS treatment, its specific course, usage of antiviral drugs with immunomodulating properties is relevant today. One of these drugs is inosine pranobex, which is able to suppress synthesis of the virus through structure of inosinic acid in polyribosomes of a cell affected by the virus, and also helps to eliminate deficiency or dysfunction of immunity, which is quite often observed in HSV infection. Today, inosine proanobex is quite actively used for genital herpes as an immunomodulator of non-specific link of immunological protection, it affects the activity of T-cytotoxic lymphocytes and natural killers, enhances the action of neutrophil granulocytes, chemotaxis and phagocytosis of monocytes and macrophages, increases the synthesis of interleukins IL-1 and IL-2, affects the number of IgG immunoglobulins [1, 2, 4].

MATERIALS AND METHODS OF RESEARCH

The study was carried out in compliance with the main provisions on human rights and biomedicine of the Council of Europe Convention, the Helsinki Declaration of the World Medical Association (1964-2008), the order of the Ministry of Health of Ukraine No. 690 of 09/23/2009. The study was approved by the Commission on Ethical Issues and Biomedical Ethics of the Poltava State Medical University (meeting No. 212 dated January 11, 2023). Voluntary written consent to participate in scientific research was obtained from all patients.

Aim of study. Analysis of drug inosine pranobex effectiveness in pharmacotherapy of herpetic stomatitis.

In the study (2015-2020), 73 patients with HS who were treated on the basis of the communal enterprise "Poltava Regional Clinical Hospital named after

M.V. Sklifosovsky of Poltava Regional Council", 31 men and 42 women specifically, age range from 18 to 54 years old. It was found that 21 people (28.8%) had first-time herpes stomatitis, 37 people (50.7%) had recurrent oral herpes, and 15 people (20.5%) had recurrent labial herpes. The study included patients with a moderate-severe form of HS. Average duration of the disease is from six months to eight years. The diagnosis was confirmed on the basis of following data: case history, patient examination, laboratory tests (HSV scraping from rash elements, determination of IgM and IgG antibodies to HSV-1) [2, 4, 14]. The basis of pharmacotherapy for HS includes: ethiotropic (antiviral), pathogenetic, symptomatic (general and local) treatment. All were prescribed the following treatment: acyclovir (Lekhim-Kharkiv, Ukraine) 200-400 mg orally 3 times a day (treatment of the first group lasted 10 days, the second group – 7 days), 5% acyclovir cream (Lekhim -Kharkiv, Ukraine) 3-5 applications per day locally, cycloferon (Biopharma, Ukraine) intramuscularly 250 mg once every 48 hours, ibuprofen (Lekhim-Kharkiv, Ukraine) 200-400 mg 3 times per day orally until the symptoms of inflammation disappear. For the purpose of detoxification therapy, patients are recommended to consume a sufficient amount of liquid [5].

Patients were divided into 2 groups. The first group received generally accepted therapy, namely 30 patients (41.09%). In the second group, inosine pranobex was added to the standard therapy at a dose of 1000 mg 4 times a day orally (the average duration of treatment was 7 days), it consisted of 43 patients (58.91%) [8, 10].

The obtained data were statistically processed using the STATISTICA 8.0 software package (serial number 31415926535897), the normality of the distribution was determined using the W-Shapiro-Wills test by calculating the mean value (M), standard error of the mean (m), significance level (p). Significance of between-group differences was assessed using two-sample Student's t-test with Bonferroni correction for independent samples and two-sample Student's t-test for dependent samples. Changes were considered statistically significant at $p \leq 0.05$ [6].

RESULTS AND DISCUSSION

Aggravation of herpetic stomatitis was accompanied by complaints of pain and rashes on oral mucosa, an increase in temperature to 38ºC-38.5ºC, general weakness. When examining the red rim of the mouth, skin of the lips, mucous membrane of cheeks, and hard palate, there were revealed blisters, erosions, and crusts. The mucous membrane was significantly hyperemic, swollen, quite painful during palpation. Submandibular lymphatic nodes were enlarged and slightly painful. Also, the aggravation of herpetic stomatitis was accompanied by changes in immunological indicators of blood before the start of treatment. This is evidenced by a decrease in the number of leukocytes by 1.3 times ($p<0.01$) and lymphocytes by 1.4 times ($p<0.001$) compared to the indicators of healthy donors. The development of herpetic disease led to a change in the lymphocyte population, in particular, the number of T-lymphocytes CD3+, CD19 decreased by 1.8 times ($p<0.001$). Against this background, the number of T-helper CD4+, CD8- and T-suppressors CD4-, CD8+ decreased by 1.9 times ($p<0.001$) and 1.7 times ($p<0.001$), respectively, compared to the indicators of healthy donors. Also, the number of CD3- and CD19+ B-lymphocytes and the ratio of the CD4/CD8 index were likely to decrease compared to healthy donors. The development of herpetic stomatitis led to a decrease in the level of IgM by 1.7 times ($p<0.001$) and an increase in the content of IgG by 1.5 times ($p<0.001$) compared to the indicators of the conventional norm.

The obtained results indicate that in herpetic stomatitis, the main parameters characterizing cellular immunity are suppressed and an imbalance of IgM and IgG content occurs. Suppression of immune response can promote spread of the virus in intercellular spaces or through cells. At the same time, an increase in IgG against the background of cellular immune reactions suppression indicates the possibility of a chronic course of viral process with inevitable relapse.

As a result, it was established that the tolerability of proposed therapy in both groups was satisfactory. Adverse reactions to prescribed drugs were not observed.

When analyzing immunological indicators in the 1st group of patients with traditional therapy, on the 5th day of the disease a slight but probable increase in the number of lymphocytes (T-lymphocytes in particular) was noted, compared to that before treatment. The number of T-helpers CD4+,CD8- increased by 1.4 times compared to the initial values. With regard to other immunological indicators, only a tendency towards their normalization was revealed relative to those before treatment.

Analysis of clinical picture dynamics in the 2nd observation group revealed almost no pain symptoms from the first day of treatment, normalization of body temperature indicators on the 2nd day of therapy, reduction of symptoms of inflammation, swelling and improvement of epithelization processes on the 3rd-4th day. Changes in immunological indicators were observed in the group of patients with the addition of

inosine pranobex to the complex treatment on the 5th day from the start of therapy. This was evidenced by an increase in the number of changes in leukocytes by 1.2 times ($p<0.05$) and lymphocytes by 1.3 times ($p<0.01$) compared to the indicators before treatment. Such therapy contributed to a probable increase in the number of T-lymphocytes by 1.4 times, in particular T-helper CD4+,CD8- by 1.7 times ($p<0.001$) and T-suppressors CD4-,CD8+ by 1.5 times ($p<0.001$) compared to patients' indicators before treatment. The proposed therapy contributed to a probable increase in CD3-, CD19+ B-lymphocytes, as well as a 1.6-fold increase ($p<0.001$) and a decrease in IgG ($p<0.01$) compared to the indicators before treatment.

It should be noted, that in the 1st group of patients on the 5th day of the disease, the indicators probably differed from the corresponding values of healthy donors. At the same time, in the 2nd group of patients with the addition of inosine pranobex, the immunological indicators probably did not differ from the control values (Table).

Influence of different treatment regimens on the immunological indicators of patients with herpetic stomatitis (M±m)

Indicator	Donors (control), n=20	Patients with herpetic stomatitis, n=73			
		before treatment 1st group	after treatment 1st group	before treatment 2nd group	after treatment 2nd group
Leukocytes, 10^6/l	5271.4±231.6	4146.3±243.6*	4567.4±213.2*	4136.2±257.7*	4844.8±219.4**
Lymphocytes, 10^6/l	2813.7±204.3	1967.4±108.3*	2311.4±116.2*·**	1973.6±104.9*	2471.9±123.5**
T-lymphocytes CD3+,CD19, 10^9/l	1.876±0.073	1.089±0.053*	1.328±0.059*·**	1.067±0.058*	1.438±0.064*·**
T-helpers CD4+, CD8-, 10^9/l	0.974±0.043	0.538±0.03*	0.736±0.04*·**	0.518±0.028*	0.863±0.038**
T-suppressors CD4-, CD8+, 10^9/l	0.769±0.034	0.463±0.021*	0.516±0.024*	0.457±0.023*	0.685±0.029**
B-lymphocytes CD3-CD19+, 10^9/l	0.316±0.017	0.210±0.015*	0.241±0.014*	0.207±0.016*	0.276±0.014**
Index CD4/CD8	1.27±0.051	0.16±0.04*	1.43±0.051	1.13±0.042*	1.26±0.049**
IgM, g/l	1.93±0.12	1.13±0.089*	1.38±0.091*	1.12±0.074 0.001	1.78±0.054 - 0.001
IgG, g/l	13.17±0.64	19.17±1.12 0.001	15.73±1.30	19.24±1.13*	17.31±1.02**

Notes: * – probable differences in comparison with the indicators of donors (control) ($p<0.05$ according to the two-sample Student's t-test with Bonferoni correction (Bonferoni test) for multiple comparisons; ** – probable differences in comparison with the indicators of patients before treatment of the corresponding group ($p<0.05$ two-sample Student's t-test for dependent samples.

The proposed complex treatment with the additional use of inosine pranobex contributed to a more active normalization of immunological indicators.

Established changes in immunological parameters are evidently the basis that in patients of the 2nd group with HS, significantly faster positive dynamics was observed, more specifically: a decrease in pain, symptoms of intoxication, general weakness, signs of gingivitis and stomatitis. Normalization of body temperature was observed in the 1st group on the 4th-5th day of treatment in 27 patients (90%), and in the second group – on the 2nd-3rd day of treatment (42 patients (95.34%)). Epithelization processes in the first group were noted on the 6-7th day, and in the second group, with inosine pranobex added to a complex treatment, the epithelization of the OM was noted on the 4-5th day from the onset of the disease.

Therefore, the recovery of the patients of the second group occurred 3 days earlier than in the 1st group without inosine pranobex usage.

The ability of inosine pranobex to exhibit a powerful immunomodulatory effect determined its use in the complex therapy of children with acute herpetic stomatitis with a severe course. In this case, the inclusion of drug led to restoration of immunological changes and accelerated the recovery of patients [4].

It should be noted that the expediency and safety of prescribing inosine pranobex for the treatment of simple herpes virus infection against the background of systemic connective tissue disease has been shown.

The clinical effectiveness of antiviral therapy in this case was confirmed by the reduction of clinical manifestations of the disease in patients with mild, moderate-severe and severe course of herpes virus infection [14].

The expediency of using our proposed treatment scheme for herpetic stomatitis is confirmed by the effectiveness of inosine pranobex in combination with acyclovir for the complex therapy of recurrent genital herpes in women. In this pathology, usage of the proposed scheme accelerated the normalization of the immune status and improvement of well-being [2].

So, as a result of the conducted research, it was found that the development of hermetic stomatitis leads to significant disorders of the immunological status of patients, and the feasibility of including inosine pranobex in the complex therapy of this pathology, with undeniable antiviral and immunomodulating action [10].

CONCLUSION

1. Addition of the immunomodulator inosine pranobex to the classical scheme leads to increasing the effectiveness of herpes stomatitis therapy, shortening the duration of treatment and hospitalization.
2. The drug inosine pranobex in a complex therapy of herpes stomatitis has clinical effectiveness and can be added to complex therapy in patients with HS of OM, as an immunomodulator.
3. In the future, we plan to investigate the effectiveness of the drug inosine pranobex in patients with primary autoinfectious stomatitis and add it to the generally accepted local treatment.

Contributors:

Lutsenko R.V. – methodology, conceptualization, writing – review and editing, project administration;

Moisieieva N.V. – data curation, validation;

Sydorenko A.H. – writing – original draft, visualization;

Ostrovska H.Yu. – conceptualization, resources;

Kapustianska A.A. – formal analysis, writing – review and editing.

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