EXPERIENCE OF IMMUNOFLAZID USE IN THE COMPLEX OF TREATMENT AND PREVENTION MEASURES DURING SEASONAL INCIDENCE INCREASE OF INFLUENZA AND ARVI

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Resume. The efficacy of Immunoflazid® (Ecopharm, Ukraine) in infants with acute respiratory viral infections was studied. The tolerability of the drug, its clinical efficacy, and the high compliance of the treatment allow the drug to be widely recommended for use in ambulatory and inpatient settings as a therapeutic and prophylactic agent.
Key words: acute respiratory viral infection, infants, Immunoflazid.

Introduction

Acute respiratory viral infections (ARVI) and influenza are the most frequent infectious pathology of childhood, the proportion of which accounts for 90% of all infectious diseases. The cause of ARVI is over 300 types of viruses. The high prevalence of acute respiratory viral infections is due to a large variety of pathogens: influenza (A, B, C), parainfluenza, adenovirus, respiratory syncytial, rhizovirus, enterovirus, and other infections.

According to WHO data, both in developed countries and in developing countries, children of the first 3 years of life have on average 6-8 ARVI per year. The total number of ARVI in preschool children is about 50 if not only heavy, but also low-intensity-infection are taken into account. Children attending kindergartens suffer from diseases especially often in the first 1-2 years. “Home” children have ARVI 10-15% less often than “organized” ones during the first 7 years of life [4].

All pathogens of ARVI show high contagiousness, because they spread by airborne transmission, damage the upper respiratory tract, and have general mechanisms for the development of infection. The penetration of the virus into the child's body is accompanied by clinical signs of irritation of the respiratory tract (the appearance of coughing, dermatitis and sore throat). The stage of development and reproduction of the virus is characterized by the development of the catarrhal syndrome (nasal congestion, undead, lacrimation). While the stage of the spread of the virus in the baby's body is accompanied by the development of symptoms of general intoxication (fever, appetite loss or refusal of food, increased fatigue, child's weakness, sleep disturbance). Reducing the symptoms of intoxication occurs only from the period or stage of activation of the immune response of the child's body. It should be noted that ARVI are often accompanied by activation of the endogenous microflora of the child. This, in its turn, can lead to the development of complications - infections of the upper respiratory tract, diseases of the ENT organs (sinusitis, otitis media). This development is particularly characteristic of infants [2.7].

ARVI in children is the most common cause of a pediatrician's house-call. ARVs in school-age children are usually benign, and in infants they may be complicated by otitis media, sinusitis, bronchitis, and pneumonia. It should be noted that the flu, unlike other ARVI, has a more severe course with the development of complications. To date, a number of risk factors for the development of frequent acute respiratory infections in children have been identified. One of these factors is the peculiarities of the development of the immune system of infants, the so-called "late start". It is known that early age is one of the critical in the life of a child. This is due to the reduction of maternal antibodies that the child received during the period of intrauterine development. While their own antibodies still do not have time to be formed to protect the child from the rapid flow of “antigenic information” that comes from the environment. An important risk factor for the development of frequent ARVI is also the anatomic-physiological features of children that make them more susceptible to infection. The most significant are the narrowness of the respiratory tract, the tendency of the mucous membrane to swelling, increased secretion. Fertile ground for the development of ARVI in children is the impact of environmental factors (nature of feeding, early socialization - early start of visiting kindergartens, passive smoking, climatic conditions, etc.) [1,3].

Despite the general pathogenetic mechanisms of development of ARVI, taking into account the prevalence and heterogeneity of the disease, it is often necessary to make a differential diagnosis in order to identify the pathogen, the choice of treatment tactics, etiotropic therapy and prevention of complications. In order to verify the diagnosis of ARVI and influenza, in addition to the clinical characteristics of the disease, laboratory diagnosis is required. Specific laboratory methods of investigation are used to verify the causative agent of the ARVI type. The value of diagnostic tests for detection of an agent is determined by their sensitivity and time spent to obtain the result. Serologic methods have limited use for the diagnosis of acute respiratory infections because they can not be used in the early stages of the disease. This is due to the fact that antibodies appear in the blood 2 weeks after infection, and by this time, sick children, as a rule, already recover, and laboratory verification of the infectious agent becomes a small actuality for the ill child.

Virusological methods enable to isolate the viruses from the patient, which makes it possible to study their biological properties. However, virological studies are the longest and most expensive method. IFA is an accessible diagnostic method, but with low sensitivity. PCR has a high sensitivity, which enables to get comprehensive information about the pathogen, to predict the nature of the course of the disease. At the same time, this is an expensive method, and the doctor receives findings of the test in most cases after 2-3 days, which makes it difficult to use it in everyday clinical practice. More and more data are available in the literature sources on the rapid methods for diagnosing viruses, pathogens of ARVI, which include immunochromatography test. The method can be used in the patient's bed. The sensitivity and specificity of this method is 90-95%, and the timing of identification of the virus can be reduced to 10-15 minutes. However, for unknown reasons, it is not available for the broad applicability in medical practice.

So, respiratory infections diagnostics takes time. It is necessary to treat a child with ARVI already in the first hours, without waiting for laboratory findings, because after 8 hours the number of replicas of the virus can reach 10^3, and by the end of the first day it amounts to 10^{27} replicas. Due to the lack of a real possibility to establish the type of infectious agent in the first 2 days of the disease, in choosing etiotropic therapy, the physician should rely only on his own experience in evaluating the symptoms of the disease and medicines for the treatment of ARVI available in the pharmaceutical market [2,6,8].

ARVIs are characterized by mass character, seasonality and cyclicity, which determines the relevance of the search, development and implementation of new means of preventing disease in children. When choosing prevention measures for ARVI, the probability of infecting children is high, which is quite high in organized groups, in points of concentration of the epidemy. The problem is of special medical and social significance also because of the significant economic costs of medicine. The purpose of numerous studies is to find new effective and safe methods of therapy and prevention of respiratory diseases [6,8].

Taking into account the above mentioned, the relevance of prevention of ARVI and influenza in children becomes clear. The most effective method of preventing infectious diseases is active specific immunization. It should be noted that the influenza vaccines have significantly reduced the incidence of influenza among the vaccinated.

Today in the arsenal of a practitioner there are also medical products for non-specific prevention of ARVI and influenza in children. However, in the presence of OTC drugs in pharmacies, the problem of self-treatment is acute. Parents independently or with the help of the Internet "prescribe" drugs to children, sometimes quite aggressive, which leads to a significant deterioration of the condition, the appearance of complications. Before treating, it is necessary to find out the cause of the disease, and this point (in essence, the question of trust in the doctor and awareness of the limits of their capabilities and their responsibility) must be communicated to parents from the very beginning of communication with them [5,8].

Taking into account the etiopathogenetic aspects of ARVI, the ways and mechanisms of infection, the drugs of choice for their treatment should have the following main pharmacodynamic properties:

- direct antiviral action at all stages of development of a viral infection;
- direct antiviral action of a wide spectrum (influenced by both RNA and DNA-viruses);
- ability to suppress neuraminidase activity of infuenza viruses;
- high bioavailability to the mucous membranes of the respiratory tract;
- antioxidant mechanism of action;
- Immunotropic effect, without the development of refractoriness of immune cells.

Absence of the latter can cause immune distress syndrome, which is characterized by successive stages: immunotoxicosis - immunodeficiency - immunoparalysis (functional failure of monocytes). Widespread use of drugs with interferon-stimulating activity can lead to the exhaustion of the immune system, the activation of other infections. In accessible literature sources, there are some evidence-based studies on

the study of immunological refractoriness when using antiviral drugs with the immunological mechanism of antiviral activity [1,2].

It should be remembered that the multiplication of viruses occurs in the "entrance gate" of the infection - epithelial cells of the upper respiratory tract. Most drugs for the prevention, treatment of ARVI are in solid form and do not have affinity to the epithelial cells of the mucous membrane of the upper respiratory tract and thus cannot protect against the virus infection at the stage of penetration of the virus into the port of infection [3].

Medicinal products with different mechanism of action were registered in the pharmaceutical market of Ukraine, which are used for the treatment of ARVI, including influenza, in children.

Plants have been used to treat viral infections since ancient times. To date, medicinal plants have not lost their relevance and popularity due to the presence of positive properties. Thus, plant medicines have mild pharmacological effect, scarcely cause side effects, are better tolerated by children and can be used for a long time, which is especially important in pediatrics. Innovative technologies enable to receive medicinal products of plant origin, which in their efficacy are not inferior to synthetic, and in some cases also have an additional anti-inflammatory effect. In addition, such phytopreparations contain a dosage amount of the active substance, which ensures the safety and effectiveness of treatment [1,2,6,8]. Immunoflazid® by "Ecopharm" company has a significantly better benefit/risk ratio than synthetic drugs. Herbal extracts contained in Immunoflazid® grass of bushgrass (Herba Calamagrostis epigeios L.) and tufted hair grass (Herba Deschampsia caespitosa L.) provide a complex pharmacological effect: a direct antiviral effect on ARVI and influenza viruses, prevent reproduction of the virus, inhibit neuraminidase activity of the influenza virus. Immunoflazid® has immunological activity, induces the synthesis of endogenous α and γ interferons, while not contributing to the refractoriness of the immune system. Using it for 6-9 months does not lead to the loss of the ability to induce α and γ-interferons by immunocompetent cells. This property of the drug retains the ability of the immune system to adequate immune protection. Immunoflazid® also has a detoxifying and anti-inflammatory effect that is compatible with antibiotics. The medical form of Immunoflazid® meets the toxicological safety requirements for children, even from the period of neonatality. Most synthetic antiviral drugs that are used both for prevention and for the treatment of ARVI have their limitations in different age groups.

The liquid dosage form of Immunoflazid® provides the admission of the active substance directly to the cells of the target organ (to the mucous membranes of the upper respiratory tract). The scheme for appointing and taking the drug is simple and understandable. Attention should be paid to the economic availability of the medicinal product, which is also a significant factor for widespread use both for prevention and for the treatment of ARVI and influenza.

The use of plant-based medicines in the treatment of ARVI is a reliable, effective and safe alternative to the use of synthetic drugs.

Thus, Immunoflazid® is a drug that fully meets the requirements for prevention and treatment of influenza and ARVI in children.

Table 1

Dynamics of the content of immune system parameters in children with ARVI (M±m)

Parameter	Group I (n=25)		Group II (n=25)	
	before treatment	after treatment	before treatment	after treatment
CD3+, %	43.1±2.1	56.9±1.0*	47.3±2.2	50.3±0.8
CD4+, %	35.1±1.2	42.7±1.2*	37.1±1.46	38.6±1.1
CD8+, %	29.4±1.8	26.5±0.7	27.9±1.7	27.1±1.0
CD16+ %	11.4±1.0	14.1±1.2*	11.0±0.9	12.3±1.1
CD4/CD8	1.2±0.1	1.6±0.8	1.3±0.2	1.4±0.7

Notes: * - significance of differences with the indicators before treatment ($p<0.05$).

The goal of the study was to evaluate the effectiveness and direction of the immunomodulating action of Immunoflazid® in the treatment of infants with acute respiratory infections of the upper and lower respiratory tract.

Material and methods of research

The criteria for the inclusion of infants in the study were the presence of acute respiratory infection of the upper and lower respiratory tract, the age of children was 1 month to 3 years. In accordance with the desired goal 50 infants were included in the study. All children were provided inpatient treatment in the department for early childhood of Vinnytsia Regional Children's Clinical Hospital. The children were divided into two groups for the study: the first (experimental) group - 25 children with acute respiratory

infection of the upper and lower respiratory tract that were administered Immunoflazid® ("Ecopharm", Ukraine) in combination with symptomatic therapy; the 2nd (comparison) group - 25 children with acute respiratory infection of the upper and lower respiratory tract that were provided symptomatic therapy. The distribution of patients in groups was carried out by random sampling. Groups were comparable in terms of age, gender, structure, and severity of the disease. Children of both groups received traditionally etiotropic and pathogenetic therapy, symptomatic therapy.

All children were provided a set of protocol and specialist studies. To assess specific parameters of the immune system, the population and subpopulation composition of lymphocytes was determined using monoclonal antibodies to $CD3^+$ (T-lymphocytes), $CD4^+$ (T-helpers), $CD8^+$ (T-cytotoxic lymphocytes), CD16+ (NK-cells) antigens. The endocrine function of the rectum gland was evaluated based on the content of the thymulin-Zn^++-binding nonapeptide in the plasma of children using the method of J.E.Bach (E.Mocchegiani et al., 1995). In order to assess the overall reactivity of the body of children, a traditional heliogram was used, by means of which the integral coefficients were calculated: cell-phagocytic protection (CFP) and specific immune lymphocytic-monocytic potential (SILMP).

The conclusion on the efficacy and tolerability of Immunoflazid® ("Ecopharm", Ukraine) was based on the analysis of objective and subjective data obtained during the study, findings of laboratory tests made in the time course of treatment and observation (before treatment and in 14 days after the start of treatment).

Immunoflazid® was used in syrup form, which was added to 5 ml (1 teaspoon) of water and was used 20-30 minutes before meals in age-correspondent doses: babies - 0.5 ml 2 times a day for 14 days; infants aged 1 to 2 years - 1 ml 2 times a day for 14 days.

The statistical analysis was performed using MS Office Excel for Windows XP. Comparison of the mean values was performed according to Student's criterion, the difference in the frequency of signs was determined using the Pearson χ^2 criterion.

Results of the study and their discussion

We conducted an analysis of the clinical and immunological efficacy of Immunoflazid® ("Ecopharm", Ukraine) in children with ARVI. The most informative clinical manifestations were: the duration of the syndrome of intoxication and respiratory syndrome, the length of stay in the hospital. Clinical parameters were recorded daily, which enabled to control the effectiveness of pharmacotherapy throughout the period of stay of children at hospital. The main laboratory parameters were determined during hospitalization of the patient and at discharge of the child from the hospital. An indicator of the effectiveness of treatment was the average length of stay of children at hospital. The findings of the study showed that the time spent in the hospital was reduced by 1.5 times in the main group of children in comparison with the control group (Group I - on average 6.02 ± 0.5 days, Group II - 12.6 ± 0.7 days ; $p<0.05$), the course of the disease was milder and the temperature period was twice as small (I gr. - an average of 4.1 ± 0.6 days, II gr. - 8.7 ± 0.7 days, $p<0.05$); the symptoms of intoxication were less pronounced and eliminated 2.5 times faster (I gr. - an average of 4.6 ± 0.3 days, II gr. - 10.6 ± 0.7 days, $p<0.05$).

Statistically significant changes in the parameters of immunological status in comparison with the indicators of children in the comparison group (Table 1) corresponded to clinical efficacy of Immunoflazid®. In children who were administered Immunoflazid® normalization of CD+ T-lymphocytes ($CD3^+$, $CD4^+$, $CD8^+$, CD16 +) and CD4/CD8 immunoregulatory index compared to baseline levels were reported. Thus, in the group of patients administered Immunoflazid®, an increase in the relative number of T-lymphocytes in the blood before the discharge was observed compared to the indicator in the comparison group ($p<0.01$). In this group of children, the normalization of $CD4^+$ T-helper cells was noted as compared to baseline (35.1 ± 1.2% versus 42.7 ± 1.2%; $p<0.05$).

The analysis of the results of the study of the dynamics of cell phagocytic protection indicators (CPPI), specific immune lymphocytic-myocytic potential (SILMP) in the examined children under the influence of immunomodulatory therapy is given above. It was found that in children of the first group of the study with the treatment with Immunoflazid® there was a significant increase in CPPI and decrease in SILMP compared to the findings before treatment ($p<0.05$). Thus, the following indicators after treatment in children in the first group were 0.701 ± 0.03 and 0.541 ± 0.05 (respectively, CPPI, SILMP). While the indicated rates in children in the second group of studies after the treatment did not significantly change ($p> 0.05$), although there was a tendency for their increase (0.63 ± 0.07 and 0.834 ± 0.06 (respectively, CPPI, SILMP) compared with the initial findings before treatment (0,598 ± 0,05 and 0,832 ± 0,04 (respectively, CPPI, SILMP)). This suggests the possibility of using these data for screening assessment of nonspecific protective factors in infants.

The cycle of Immunoflazid® in ARVI treatment in infants also contributed to the normalization of the level of thymulin and prevented the further reduction of the mass of the substernal gland. Thus, in the children group that was administered Immunoflazid®, the increase in the level of thymulin was 53.6% ($p<0.05$). Whereas in the second group of children the level of thymulin in serum was significantly lowered by 32.3% during the treatment period ($p<0.05$). The assignment of Immunoflazid® resulted in a significant increase in the blood serum level of thymulin in children with ARVI (4.7±0.1 log2), which was higher than that in the comparison group, where the content of thymulin significantly decreased (2.1±0.2 log2; $p <0.05$). Consequently, the dynamics of the content of thymulin in serum adequately reflected changes in the morphometric parameters of the substernal gland in the course of treatment. All children who took Immunoflazid®, tolerated the treatment well. No side effects were reported. The study showed that with the use of backbone therapy, full clinical efficacy was noted in 6 (24.0%) children, and in 9 (36.0%) children when Immunoflazid® was included in the therapy. In general, when using Immunoflazid® in 68.0% of infants, the positive dynamics of the course of ARVI was detected.

Conclusions

The use of Immunoflazid® in infants with acute respiratory infections and influenza helps to restore the functional state of thymus (normalization of the level of thymulin), T-cell parameters of immunity, integral coefficients of nonspecific protection factors ($p<0,05$). Inclusion of Immunoflazid® in the treatment of acute respiratory infections in infants helps to reduce the length of stay at hospital ($p<0,05$). The above listed previously known and new therapeutic effects of Immunoflazid® give grounds for its wide use in children with ARVI and influenza. Immunoflazid® is a drug that fully meets the etiopathogenetic requirements of the prevention and treatment of acute viral infections in children.

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