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Ефективність превентивного використання флавоноїдів у дітей шкільного віку в комплексі заходів щодо зниження захворюваності на гострі респіраторні захворювання

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Мета: вивчити клініко-імунологічну ефективність превентивного використання флавоноїдів (Імунофлазид®, Протефлазид®) у дітей шкільного віку в комплексі заходів щодо зниження захворюваності на гострі респіраторні захворювання (ГРЗ).

Пацієнти та методи. 78 дітей віком від 7 до 17 років для профілактики ГРЗ отримували протефлазид (дітям до 9 років застосовувався сироп Імунофлазид, а дітям від 9 і старше — Протефлазид відповідно до вікових доз та інструкції виробника) у сезоні різних календарних років. Тривалість сезонної профілактики ГРЗ для всіх дітей склала два тижні. Клінічну ефективність включення флавоноїдів до сезонної профілактики оцінювали за інтенсивністю та перебігом ГРЗ, динамікою стану біоценозу слизових верхніх дихальних шляхів та за результатами імунологічного обстеження: лейкоцити, лімфоцити, CD25+, IgA, IgM, IgG, TFβ₁ (DRG ELISA, Germany), IL-4, IL-10, IL-12p70 і IL-12p40+p70 (ELISA, Diacclone, France), IL-2 (ELISA Kit, Finland) у сироватці крові. Математична обробка результатів дослідження проводилася з використанням статистичних програм Statgraf, Matstat, Microsoft Excel для Windows, з використанням пара- і непараметричних критеріїв достовірності.

Результати. Проведення профілактичних заходів у дітей шкільного віку з використанням протефлазиду (Імунофлазид®, Протефлазид®) дозволяє зменшити кратність ГРЗ у 1,2–1,5 разу, а у випадку захворювання — знизити тривалість гострого респіраторного епізоду на 1,8–2,2 дня. Усі ГРЗ, що виникають, характеризуються більш легким перебігом. Ефективність превентивної профілактики ГРЗ у дітей 7–17 років з використанням сиропу Імунофлазид® або крапель Протефлазид® в середньому складає 82% та характеризується хорошою переносимістю, призводить до формування стану еубіозу слизових ВДШ у 64,1% випадків. Одним з основних імунологічних ефектів протефлазиду (Імунофлазид®, Протефлазид®) є його здатність превентивно контролювати можливість пролонгування запального процесу на імунологічному рівні у дітей шкільного віку.

Висновки. У схемах профілактики сезонних ГРЗ у дітей шкільного віку використанням протефлазиду є ефективним та доцільним.

Ключові слова: гострі респіраторні захворювання, діти, профілактика, протефлазид.

The efficacy of the preventive usage of flavonoids among the school age children in the complex reduction of the acute respiratory diseases incidence

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Objective: to study the clinical and immunological efficacy of flavonoids use (Imunoflazid®, Proteflazid®) with preventive purpose in school age children in a complex of measures to reduce the incidence of acute respiratory diseases.

Materials and methods. A total of 78 children aged 7 to 17 years, for the prevention of acute respiratory disease were assigned Proteflazid (children up to the age of 9 used the Imunoflazid syrup, and children older than 9 were administrated Proteflazide, in a dose corresponding to the manufacturer's medicinal product label) in the season of different calendar years. The duration of seasonal prevention of ARI for all children was 2 weeks. Clinical efficacy of the flavonoids entry in the seasonal prevention regimen was assessed by the intensity and course of acute respiratory disease, the dynamics of the mucocutaneous biocenosis of the upper respiratory tract. The immunological examination (leukocytes, lymphocytes, CD25 +, IgA, IgM, IgG, TFβ₁ (DRG ELISA, Germany), IL-4, IL-10, IL-12p70 and IL-12p40 + p70 (ELISA, Diacclone, France), IL-2 (ELISA Kit, Finland) in serum) was used for appraisal as well. Statistical analysis of the research results was carried out by using of the statistical programs Statgraf, Matstat, Microsoft Excel for Windows, and by applying para- and nonparametric reliability criteria.

Results. Carrying out the preventive measures in children of school age using Proteflazide (Imunoflazid®, Proteflazid®) makes it possible to reduce the incidence of acute respiratory infections by 1.2_1.5 times, and in case of disease, reduce the duration of an acute respiratory episode by 1.8_2.2 days. In addition, all emerging acute respiratory infections had low_grade severity. The efficacy of ARI preventive prophylaxis in children aged 7–17 years with Imunoflazid® syrup or Proteflazide® drops made up in average 82%, was characterized as well_tolerated, and provided the formation of eubiosis of the upper respiratory tract mucous membranes in 64.1% of cases. One of the main immunological effects of Proteflazide (Imunoflazid®, Proteflazid®) is its preventive control the possibility of inflammatory process prolonging at the immunological level in school age children.

Conclusions: the use of Proteflazide in the prophylactic regimens of seasonal ARI in school age children is effective and appropriate.

Key words: acute respiratory diseases, children, prophylaxis, Proteflazide.

Эффективность превентивного использования флавоноидов у детей школьного возраста в комплексе мер по снижению заболеваемости острыми респираторными заболеваниями

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Цель: изучить клинико-иммунологическую эффективность превентивного использования флавоноидов (Имунофлазид®, Протефлазид®) у детей школьного возраста в комплексе мероприятий по снижению заболеваемости острыми респираторными заболеваниями (ОРЗ).

Пациенты и методы. 78 детей в возрасте от 7 до 17 лет для профилактики ОРЗ получали протефлазид (детям до 9 лет применялся сироп Имунофлазид®, а детям от 9 и старше — Протефлазид®, в дозе, соответствующей инструкции производителя) в сезоне разных календарных лет. Продолжительность сезонной профилактики ОРЗ у всех детей составила две недели. Клиническую эффективность включения флавоноидов в схему сезонной профилактики оценивали по интенсивности и течению ОРЗ, динамике состояния биоценоза слизистых верхних дыхательных путей и по результатам иммунологического обследования (лейкоциты, лимфоциты, CD25+, IgA, IgM, IgG, TF α (DRG ELISA, Germany), IL-4, IL-10, IL-12p70 и IL-12p40 + p70 (ELISA, Diaclone, France), IL-2 (ELISA Kit, Finland) в сыворотке крови). Математическая обработка результатов исследования проводилась с применением статистических программ Statgraf, Matstat, Microsoft Excel для Windows, с использованием пара- и непараметрических критериев достоверности.

Результаты. Проведение профилактических мероприятий у детей школьного возраста с использованием протефлазида (Имунофлазид®, Протефлазид®) позволяет уменьшить кратность ОРЗ в 1,2–1,5 раза, а в случае заболевания — снизить продолжительность острого респираторного эпизода на 1,8–2,2 дня. К тому же все возникающие ОРЗ имели более легкое течение. Эффективность превентивной профилактики ОРЗ у детей 7–17 лет с использованием сиропа Имунофлазид® или капель Протефлазид® в среднем составила 82%, характеризовалась хорошей переносимостью, также результатом профилактики было формирование состояния зубиоза слизистых верхних дыхательных путей в 64,1% случаев. Одним из основных иммунологических эффектов протефлазида (Имунофлазид®, Протефлазид®) является его способность превентивно контролировать возможность пролонгации воспалительного процесса на иммунологическом уровне у детей школьного возраста.

Выводы. В схемах профилактики сезонных ОРЗ у детей школьного возраста использование протефлазида является эффективным и целесообразным.

Ключевые слова: острые респираторные заболевания, дети, профилактика, протефлазид.

Introduction

Today, in the practice of primary care physicians and pediatricians, there are many tools and schemes that are aimed at preventing acute respiratory infections (ARIs). The choice of a drug class is most often based on data concerning efficacy and safety, in particular with provision for the predicted effect of the therapeutic agent on the state of the child's immune system [4,8,9]. One of the best methods for prevention of ARIs is immunomodulation the essence of which is to achieve a balance in the functioning of the immune system of the patient by means of multi-directional effects of the drug components [1,8,9] which in the clinical findings will be manifested as a warning of primary manifestations of clinical signs or relapse of the disease [2,3,6,10,11].

The choice of the drug and its regimen to prevent ARIs in children is still a difficult task since the list of active substances and drugs that can be preventively applied to prevent ARIs is quite large and is constantly increasing but the choice of practitioner physician should be based on evidence-based medicine [2,6,7].

Our analytical review of the literature and the existing evidence base with regard to the effectiveness of the use of natural bioflavonoids, namely the active ingredient протефлазид (drugs Immunoflazid® Syrup and Proteplazid® Drops) [1-4,6-11], allow to confirm the aetiologically and pathogenetically reasonable prescription of bioflavonoids in both ARI's treatment and prevention regimens due to the presence of a direct antiviral action and antioxidant action in conjunction with immunoregulation properties as well as proven high efficacy and safety in the

case of viral and viral-bacterial diseases in children.

The aim of the study was to examine the clinico-immunological efficacy of the preventive use of bioflavonoids (Immunoflazid®, Proteflazid®) in the school-age children according to a set of measures to reduce the incidence of AIRs.

Material and methods of research

Under the supervision, there were 78 children aged from 7 to 17 years old (average age of 12.1 ± 0.3 years), namely 44 (56.4%) boys and 34 (43.6%) girls. For the prevention of ARIs, all children received протефлазид (Immunoflazid®, Proteflazid®) during the season in different calendar years - 38 children received prophylactic therapy in one of the autumn seasons (average age of 12.2 ± 0.4 years), in the other season - 40 children (12.1 ± 0.5 years; $p > 0.90$ between seasons) the affinity of which allows to combine the results for the creation of final conclusions.

According to the goal, 68 of these 78 children received one-time preventive therapy, and 10 persons with recurrent ARI received preventive therapy twice, with 12 months interval.

Children under 9 years old recieved Immunoflazid® syrup, and children aged 10 years and older recieved Proteflazid® according to age-related doses and manufacturer's instructions. The duration of seasonal prevention of ARIs for all children was two weeks.

Clinical efficacy of the inclusion of flavonoides in the seasonal prophylaxis was assessed according to the ARI intensity (the results of catamnestic observation within one or

two years after the completion of the prophylactic measures), the dynamics of the biocenosis state of the upper respiratory tract (URT) mucous membrane, the evaluation of the clinical characteristics of the course of ARI in the catamnestic observation, and the results of an immunological examination in the dynamics.

For all the children under observation the following extent of examinations was conducted:

- analysis of anamnestic data, evaluation of objective data before and after the course of prophylactic therapy, catamnestic monitoring of children after the prophylactic course of protefilazid;
- twice microbiological study of colonization of the mucous membranes of pharynx and nose in the treatment dynamics: before and after prophylactic use of proteflazid;
- immunological status was evaluated according to content of leukocytes, lymphocytes, CD25+, IgA, IgM, IgG, TFβ1 level (DRG ELISA, Germany), content of IL-4, IL-10, IL-12r70 and IL-12r40+p70 cytokines (ELISA, Diaclone, France), IL-2 (ELISA Kit, Finland) in serum before and after the prophylactic course of protefilazid.

Mathematical processing of the study results was carried out using statistical programs Statgraf, Matstat, Microsoft Excel for Windows, and when examining the significance of the reliability of statistical samples, both para- and non-parametric reliability criteria were used [5].

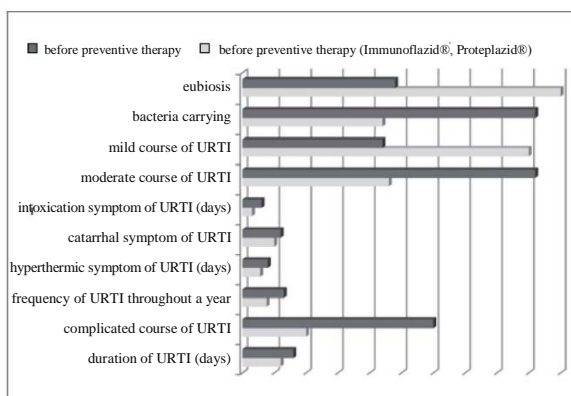


Fig. 1. Clinical efficacy of the preventive course of bioflavonoids (Immunoflazid®, Proteflazid®) in the prevention regimen of seasonal ARD in school-aged children

Results of the research and their discussion

The catamnestic observation of all children who were under the supervision during the year after inclusion in the seasonal prophylaxis program of proteflazid (Immunoflazid®, Proteflazid®) made it possible to conclude that the efficacy of preventive prophylaxis with bioflavonoids in children was 82% on average, due to a reduction in the multiplicity of ARIs in 1.2-1.5 times, and the reduction of the acute respiratory episode duration from 1.8 to 2.2 days (Fig. 1).

Along with the decrease in the ARI frequency in school-age children, a reduction by 30% in the number of cases of complicated progression of ARIs was registered. Also, in every second child who, at the beginning of the season, received preventive therapy of proteflazid (Immunoflazid®, Proteflazid®) but after some time, because of the high ARD incidence in the population, still have ARD, there was no formation of a moderate or severe course (Fig. 1).

It should be noted that in the group of children who had recurrent ARDs (10 (12.8%) persons) and received preventive treatment with proteflazid (Immunoflazid®, Proteflazid®) twice at 12 months intervals, in the catamnestic observation within a year after each preventive use of these bioflavonoids, the frequency of ARD was reduced to the level of that in children who are episodically ill which meets the criteria for the morbidity of an almost healthy child (only 1-2 episodes of ARD during the period of the catamnestic observation). And two of these 10 children did not get sick during the year.

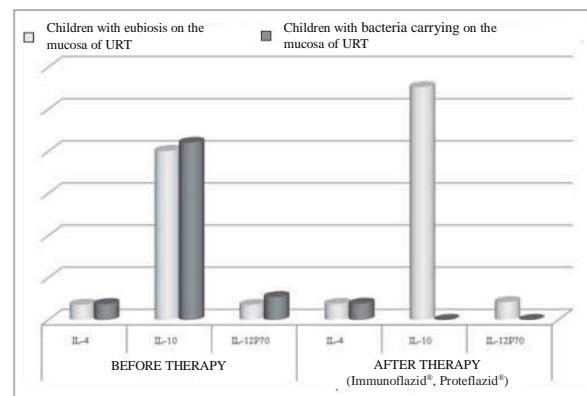


Fig. 2. Immunological efficacy of therapy with bioflavonoids (Immunoflazid®, Proteflazid®) in school-aged children depending on the state of colonization of mucous membranes of URT

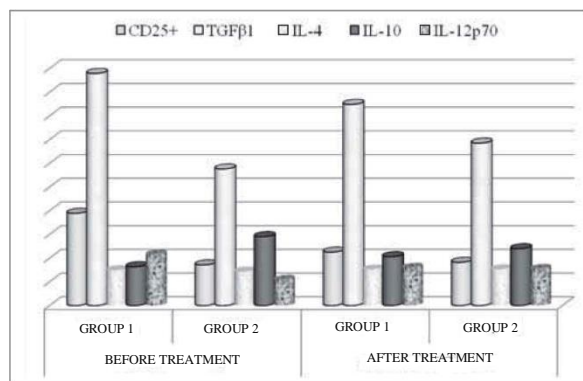


Fig. 3. Dynamics of immunological parameters in school-aged children depending on the cytokine balance against the correction with bioflavonoids (Immunoflazid[®], Proteflazid[®])

Investigation of the biocenosis state of the mucous membranes of the pharynx and nose in all school-age children in the state of clinical well-being before the prophylaxis with bioflavonoids (Immunoflazid[®], Proteflazid[®]) showed that only in 24 (30.8%) children normal flora was sowed which corresponded to the state of eubiosis of the upper respiratory tract, in other cases, the presence of opportunistic pathogenic and pathogenic flora on mucous membranes of URT was identified, the bacteriological verification of which showed that the first place took isolation of *St. Aureus* (60.4%), and the second place - *Str. Haemolyticus* (35.4%).

Control microbiological studies of the biocenosis state of the mucous membranes of URT (Fig. 1) in children immediately after completion of the prophylactic use of bioflavonoids (Immunoflazid[®], Proteflazid[®]) showed the formation of eubiosis in the majority of observations, 64.1% (n = 50) versus 30.8% (n = 24) before the start of preventive therapy (p<0.001).

Our previous studies regarding the effect of alteration of URT microbiocenosis on the state of the immune system in children-bacterial carriers in the form of their prolonged low-level inflammatory Th1-associated response, led to conduction of a comparative analysis of immunological efficacy of bioflavonoids in children that were under our supervision, depending on the colonization state of mucous membranes (Fig. 2).

According to the results of this study, after completion of the preventive course of bioflavonoids (Immunoflazid[®], Proteflazid[®]) (Fig. 2), immunological changes were recorded in children-bacterial carriers due to a possible increase in the IL-10 content (t = 2.04; p < 0.05)

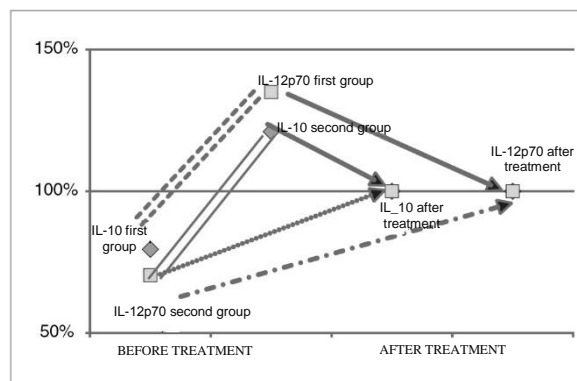


Fig. 4. Effect of bioflavonoids (Immunoflazid[®], Proteflazid[®]) on the balance of pro- and anti-inflammatory cytokines in the groups of children depending on the initial serum level of IL-12p70

and a decrease in the IL-12r70 content in serum (t = 3.5; p < 0.01) which suggests a modulating effect of bioflavonoids through the regulation of the activity of pro- and anti-inflammatory interleukins (p < 0.01).

According to our data, the immunological status of school-aged children in the period of clinical well-being and before the start of preventive measures to reduce seasonal ARD was characterized by unstable manifestations of insufficiency of various parts of the immune system that are quite varied and indicative, first of all, of the imbalance of regulatory and intensity levels in immune protection mechanisms. Therefore, the evaluation of the immunological effectiveness of the inclusion of bioflavonoids (Immunoflazid[®], Proteflazid[®]) in preventive prophylaxis of ARD in school-aged children was carried out in groups of children who differed in the nature of prophylactic and anti-inflammatory interleukin orientation, namely in 35 school-aged children with a relatively high initial level of IL-12r70 (first observation group) and 43 children with a relatively low initial level of IL-12r70 (second observation group). According to the results obtained (Fig. 3), the inclusion of bioflavonoids (Immunoflazid[®], Proteflazid[®]) into the seasonal prophylaxis of ARD in children of the first observation group resulted in a possible decrease in the IL-12r70 content (t = 4.03; p < 0.001) against the possible increase in the anti-inflammatory IL-10 content (t = 2.3, p < 0.05), while the IL-4 content in the blood serum of these children was almost unchanged (p > 0.05). In children of the second observation group (Fig. 3), the effect of bioflavonoids was realized at the expense of a possible increase in the IL-12r70 content (t = 2.23; p < 0.05), whereas the IL-4 and

IL-10 contents in serum did not change ($p > 0.05$).

Comparison of the results of immune study in school-age children after completion of the prophylactic course of bioflavonoids (Immunoflazid[®], Proteflazid[®]) (Fig. 3) did not reveal any likely differences between the levels of IL-4, IL-10 and IL-12r70 interleukins in the blood of children of both groups ($p > 0.05$), suggesting that the distribution of cytokines as the resultant characteristic of the modulating action of flavonoids is the same, as graphically represented in Fig. 4. Effect of the Immunoflazid[®] syrup and Proteflazid[®] drops on the IL-12r70 contents is mediated through the modulation of the IL-10 content in such a way that at high initial levels of pro-inflammatory IL-12r70, bioflavonoids inhibit and, at low levels, activate production of anti-inflammatory IL-10, which, in our opinion and taking into account the theoretical studies of the molecular effects of cytokine regulation, most likely, balances the Th1- and Th2-response in school-age children through regulation of the activity of the STAT-3 transcription factors which causes the normalization of the IL-12r70 serum level after completion of immune correction with bioflavonoids.

That is, proteflazid (Immunoflazid[®], Proteflazid[®]), regardless of the initial serum level of IL-12r70, modulates its concentration in serum: if its level before the correction was high, it reduces it to the average, and if it was low, then, on the contrary, increases after correction. Taking into account that proinflammatory IL-12r70 supports the development of inflammation in the body, it can be argued that one of the main immunological effects of proteflazid (Immunoflazid[®], Proteflazid[®]) is its ability to preventively control the possibility of prolonging the inflammatory process at the immunological level in school-age children.

According to our data, all children who received proteflazid (Immunoflazid[®], Proteflazid[®]) well-tolerated drugs, allergic and any adverse reactions were not observed in any one of the children.

Thus, the inclusion of bioflavonoids produced by natural synthesis (Immunoflazid[®], Proteflazid[®]) into preventive seasonal prophylaxis of ARD in school-aged children is a safe and effective measure as evidenced by

proven influence on the parameters of immunological status, is accompanied by the restoration of microecology of the URT mucous membranes and has clinically confirmed effectiveness. This allows to recommend the use of proteflazid in the seasonal prevention regimens of acute respiratory diseases.

Conclusions

1. School-age children of in the period of clinical well-being do not have stable manifestations of insufficiency of different parts of the immune system, are quite varied, that is indicative of the imbalance of regulatory and intensity levels of the immune protection mechanisms.

2. In 69.2% of school-age children in the period of somatic health, bacteria carrying was registered due to the sowing of *St. aureus* and *Str. haemolyticus* on URT mucous membranes.

3. Conducting the preventive measures in school-age children with proteflazid (Immunoflazid[®], Proteflazid[®]) can reduce the incidence of ARD in 1.2-1.5 times, and, in the case of the disease, reduce the duration of acute respiratory episode by 1.8-2.2 days. All emerging ARDs are characterized by a mild course (no formation of a moderate or severe course).

4. Preventive use of bioflavonoids (Immunoflazid[®], Proteflazid[®]) leads to the formation of eubiosis state of URT mucosa in 64.1% of cases.

5. One of the main immunologic effects of proteflazid (Immunoflazid[®], Proteflazid[®]) is its ability to preventively control the possibility of prolonging the inflammatory process at the immunological level in school-age children.

6. Effectiveness of preventive prophylaxis of ARD in children aged 7-17 years using Immunoflazid[®] syrup or Proteflazid[®] drops is 82% in average and is characterized by good tolerance indicating the high safety of these drugs.

Prospects for further research. In view of our own data and literature data regarding the components of action of bioflavonoids (proteflazid) on the human body, further studies on the adaptive properties of these compounds at different levels of adaptation of the organism are promising and substantiated.

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