SELECTION OF BIOFLAVONOIDS IN TREATMENT AND PREVENTION OF ARVI IN CHILDREN

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INTRODUCTION

Today, as well as through much of almost the entire period of survival of mankind, influenza and acute respiratory viral infections (ARVI) is a topical problem of medicine, as they are characterized by massive involvement, seasonality and perennial cyclicity and affect at least 25% of the world's population annually. According to WHO, influenza and ARVI is one of the main causes of death in the world - up to four million people die every year, and therefore the need to find effec¬tive treatment and preventive measures of this group of infectious diseases is in no doubt; it is an urgent task of modern science. Providing effective and efficient control of influenza and ARVI is an unsolved task even at the level of modern medicine, primarily due to the high proportion and prevalence of ARVI, the aetiological spectrum of which consists of more than two hundred respiratory virus types that objectively confound the etiotropic treatment of this category of diseases.

In children who are most vulnerable to the respiratory infection morbidity, the choice of drugs for prevention and treatment of influenza and ARVI is still a challenging task in the medical practice, because the drugs and active substances list that can be administered is plenty large enough and constantly mount. In medicine of the 21st century, one of the instruments of a scientifically based and meaningful choice of the intelligent and correct decision of this problem is evidence-based medicine [2, 5, 7].

Our analysis of systematic literature reviews on the treatment and prevention of ARVI, meta-analysis data, pre- and post-clinical studies outcomes, which have a high evidence level, made it possible to state that the administration of bioflavonoids is aetiologically and pathogenetically substantiated, in particular proteflazid ethanolic extract (the main active ingredient - flavonoid glycosides) and pharmaceutical dosage forms based on it - Imoflazid®, Proteflazid® with proven direct antiviral action, immunocorrecting properties, antioxidative activity, and highly efficient and safe to use in children, pregnant women and adults [1-9, 11, 12].

The ethanolic extract proteflazid, obtained by the technology of alcoholic extraction of herbal raw material of two wild grasses - tufted hair grass (Deschampsia caespitosa L.) and bushgrass (Calamagrostis epigeios L.), is a multicomponent mixture of natural compounds - chlorophyll, amino acids, flavonoid glycosides, carboxylic acids and other additional compounds. In 2002, based on 100% extract of proteflazid, a pharmaceutical product Proteflazid® drops (90% ethanol solution) was registered, and in 2006 - Imunoflazid® syrup with 2% of proteflazid extract for children from neonatal age was created [6].

The evidence base of proteflazid is unique: more than ten literature reviews (from 2008 to 2016); 4 meta-analyses (from 2014 to 2016), 15 reports and scientific publications on the clinical trials outcomes conducted during the period of 2003–2015 on the basis of medical institutions of Ukraine with the participation of more than 1150 persons, including more than 970 children aged from 0 to 18 years, 74 reports and scientific publications of the clinical studies outcomes conducted during the period of 2002-2015 on the basis of medical institutions of Ukraine and Russia with the participation of more than 3150 individuals, including: children (of all ages) - more than 900, pregnant women - more than 330 persons.

Objective: to study the clinical and immunological efficacy of the preventive administration of various dosage forms of the active ingredient of proteflazid, namely - Imunoflazid® syrup in children aged from 4 to 9 years and Proteflazid® drops in children aged 9 to 17 years - for seasonal prevention of influenza and ARVI.

MATERIALS AND METHODS

In total 91 children aged from 4 to 17 years were enrolled in the observational follow-up study. A compulsory condition of enrolment to study groups was the physical examination results that allow confirming the absence of any clinical signs of ARVI or an acute exacerbation of chronic disease in a child.

Distribution in the study groups was carried out according to the age and depending on the prescription of bioflavonoids in the form of syrup or drops. The first study group included 39 children aged 4 to 9 years who were administered Imunoflazid® syrup in the prevention regimen; the second study group comprised 52 children aged from 9 to 17 years who were administered Proteflazid® drops for the seasonal flu and ARVI prophylaxis. The duration of seasonal prevention of ARVI in this study was 2 weeks. Imunoflazid® syrup and Proteflazid® drops were assigned in accordance with the child's age and in compliance with the manufacturer's instructions.

All followed-up children were analysed by anamnestic and physical examination data. Mucosal biotope microecology of the upper respiratory tract and immune status (WBC, lymphocytes, CD25+, IgA, IgM, IgG, TFβ1 level (DRG ELISA, Germany), cytokines IL-4, IL-10, IL-12p70 and IL-12p40+p70 (ELISA, Diaclone, France), IL-2 (ELISA kit, Finland) in serum) were studied during the follow-up control of treatment doubly: before and after the prophylactic use of the agents with proteflazid.

The adaptation level was determined by the functional change index (FCI), which was calculated using the following formula: FCI=0.011 • HR + 0.014 • SBP + 0.08 • DBP +0.014 • AGE + 0.009 • WIEGHT – 0.009 • HEIGHT – 0.27, and was assessed according to the authors' recommendations (patent No. 26173; L.V. Kvashnina et al., 2005). Psychophysiological study allowed determining the type of temperament of the examined children and assessing the steady character traits of their behaviour and emotional response (Eysenck test (Gorbatov, 2003; Raihorodskyi, 2002)) and identifying the stable response as a basic stable personality characteristic. The type, performance efficiency, and the nervous system resistance in the examined children were determined using the tapping test of E.P. Ilin (Ilin, 1981).

The clinical efficacy of the flavonoids inclusion for seasonal prophylaxis was evaluated by the ARVI intensity (results of the observational follow-up study for a year or two after the preventive measures completion), the biocenosis condition of the upper respiratory tract (URT) mucosa, the clinical characteristics of ARVI during the follow-up care, the immunological profile, and the psychophysiological indicators as well.

Statistical processing of study outcomes was carried out using the licensed program Statistica v. 6.1 (serial number AJAR 909 E415822FA) with the parametric and non-parametric tests. The correlation between the factors was estimated by Spearman's rank correlation coefficient (r), the odds ratio and its 95% confidence interval. To build models of the adaptability degree and maladaptation risk prediction in children, depending upon wide range of factors, the Bayes theorem and sequential Wald analysis with the calculation of the Kullback information measure (I) and logistic regression were used. Three levels of statistical significance of study outcomes were used $p<0.05$; $p<0.01$ and $p<0.001$; at $p<0.1$, the trend was determined [10].

RESULTS AND DISCUSSION

The conducted study was dynamic provided during the season of two different calendar years with observational follow-up over the next two years. The groups of the examined children were representative and comparable, which resulted in the combining the outcomes of different years of follow-up monitoring to form the final conclusions.

The adaptation model in the examined children was as follows an integration of the close cross-system correlation relationships between clinical and anamnestic factors (physical development, bacterial carriage, acute respiratory diseases incidence in child's history, chronic foci of infection, smoking in adolescents, etc.), immunological profile (cytokine profile IL-2, IL-4, IL-10, IL-12p70, IL-12p40+p70, TGFβ_1; serum immunoglobulins A, M, G and sIgA) and the personality psychological features (such individual typological ones as temperament, character, tapping test; the presence of the border neurotic disorders; the emotional profile: high anxiety, colour choice, etc.).

The study of cytokine balance in schoolchildren showed that it was IL-10 concentration particularly, physiologically associated with anti-inflammatory properties, which determined the adaptation level of the examined children ($p=0.042$; $r=-0.264$), that correlated to the asthenic syndrome in the clinic of children with recurrent ARVI, primarily due to performance impairment ($p=0.035$; $r=0.273$) and smoking in adolescents ($p=0.023$; $r=-0.293$). The IL-12p70 concentration, which was significantly higher in children who were carriers of opportunistic pathogenic and pathogenic microflora on the upper respiratory tract mucosa, correlated with asthenic syndrome manifestations that primarily indicated the general exhaustion of children with recurrent ARVI (increased fatigability ($p=0.004$; $r=0.367$), difficulty remembering ($p=0.004$; $r=0.368$), decreased appetite ($p = 0.002$; $r=-0.395$)) and history of adeno- or tonsillectomy ($p=0.004$; $r=0.367$), which determined a low anti-infectious protection level

of these children. IL-12 is a pro-inflammatory cytokine and a key element in enhancing the cell-mediated immune response and initiation of effective anti-infectious protection against viruses, bacteria, fungi, and protozoa.

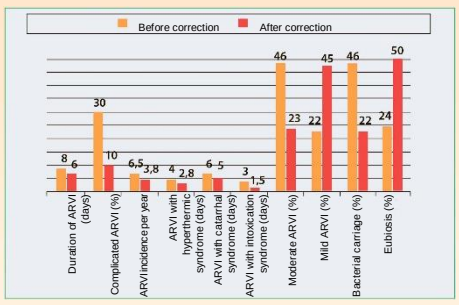

Figure 1. Clinical efficacy of the preventive course of flavonoids in the seasonal ARVI prophylaxis regimen in children of different ages

An adaptive capability evaluation of children aged 4–17 years during the period with no clinical manifestations showed that in some patients there was different level of adaptation disorders corresponding to a mixed type of desadaptative syndrome (a combination of the difficulties of psycho-physiological adaptation, cytokine imbalance at the immune response level and dysbiosis of the pharyngeal and nasal mucous membranes). It should be noted that children who had a recurrent ARVI and asthenic syndrome manifestations (prevailed complaints of sleep disorder, frustration, increased fatigability and headache) showed an unsatisfactory level of FCI and adaptation failure, and almost every third child had manifestations of adaptation stress, which allowed diagnosing a low functional reserve of the macroorganism that necessitated the implementation of corrective treatment programs and mandatory preventive measu¬res for all children.

According to our data, all children who were administered Imunoflazid® syrup and Proteflazid® drops tole¬rated the medication well, with no allergic or adverse reactions in any child.

Outcome analysis of the follow-up control of children aged from 4 to 17 years for three years showed that the therapeutic and preventive activiti¬es caused the adaptation level increasing and improving health status of the followed-up patients. It should be noted that a significant improvement was recorded in 35.2% of all observations, and additionally, positive changes were observed for 2-3 years minimally after two courses of preventive seasonal immune treatment with Imunoflazid® syrup and Proteflazid® drops. Depending upon the severity of adaptation disorders and immunity features in the examined children, there was a need to readministration of pharmaceutical preparations with proteflazid in the next calendar season to achieve an improvement effect in 30% of cases. Also, an evaluation of the child's immunobiological resistance level showed that during the observational follow-up study, the degrading effect was not registered in any child.

Generalization of the estimated results of the preventive usage efficacy of Imunoflazid® and Proteflazid® showed that in the group of children with recurrent ARVI, the number of children with good adaptation significantly (8-fold) increased and there were no cases of adaptation failure ($p<0.001$).

This study outcome analysis and generalisation based on the statistical processing of all the data obtained showed that, irrespective of age of the children examined and the use of different dosage forms of the proteflazid extract Imunoflazid® syrup in children aged 4-9 years and Proteflazid® drops in children aged from 9 to 17 years – the clinical efficacy of influenza and ARVI seasonal prophylaxis, as well as the microecology changes in the upper respiratory tract mucosa and immune components had statistical parallels (which is primarily associated with the use of the same standard base of the ethanol extract of proteflazid, regardless of its pharmaceutical form and presentation – syrup or drops), which allowed combining all the data to draw final conclusions based on the study outcomes in the further study description. The only difference was the organoleptic preferences among the examined children, in particular: Imunoflazid® syrup, according to the parents of children aged 4-6 years and the primary school-aged children themselves, aged 6-8 years, was more pleasant than drops, and in contrast children over 9 years old chose drops that they explained by a need to take a smaller amount of preparation during a two-week course of preventive treatment.

Observational follow-up study over a two-year period of all children showed that the preventive efficacy of bioflavonoids in all children (Fig. 1) who were administered preparations with proteflazid (Imunoflazid®, Proteflazid®) made up 82% on average due to a decrease in the incidence (1.7-fold) and duration (by 2 days) of ARVI ($p<0.01$).

Along with the decreasing ARVI incidence in children aged from 4 to 17 years (Fig. 1), who were followed-up, there was a milder disease in cases of ARVI that failed to prevent as compared with the severity of comparable cases of ARVI occurred during the period before preventive proteflazid administration (Imunoflazid®, Proteflazid®) due to three-fold reduction of complicated cases of ARVI, besides every second child had mild, but not moderate or severe, ARVI in cases, which failed to prevent (Fig. 1).

It should be noted that in 13 children (30%) aged from 4 to 9 years, who had a recurrent ARVI and during two consecutive seasons of the follow-up were administered namely Imunoflazid® syrup for preventive treatment, during the follow-up monitoring after each prophylactic course of bioflavonoids, a decrease in the ARVI incidence to the level of rarely ill children was detected, and this is only 1-2 ARVI episodes versus 4-6 ones prior to the preventive care onset ($p<0.01$), moreover, 3 children had no disease for a year at all ($p<0.05$).

Control microbiological studies of the mucosal biocenosis of the upper respiratory tract (Fig. 1) in children immediately after the end of the prophylactic use of bioflavonoids (Imunoflazid®, Proteflazid®) revealed the eubiosis in most cases 50 versus 24% of the observations at the baseline ($p<0.001$).

In our previous works [3], it was proved that the main immunological effect of proteflazid (Imunoflazid®, Proteflazid®) in school-aged children is its ability to control the inflammatory process prolongation at the immunological level by the cytokine profile modulating and balancing that prevents further recurrence or chronization of infection ($p<0.05$). So, at the initial high serum level of IL-12p70, proteflazid reduces it to medium ($t=3.5$; $p<0.01$), and if it was low, then, on the cont¬rary, the proteflazid administration increases its level ($t=2.23$; $p<0.05$).

Therefore, the administration of bioflavonoids in the form of Imunoflazid® and Proteflazid® preparations for seasonal ARVI prevention in school- and preschool-aged children is a safe and efficient treatment, confirmed by a proven effect on the child's adaptation and immune status, accompanied by the normalization of mucosal microecology of the upper respiratory tract and has a clinically proven efficacy, which allows to recommend their use for the seasonal prevention of ARVI incidence, especially in a patient cohort with recurrent respi¬ratory diseases.

CONCLUSIONS

1. The evaluation of the child's immunobiological resistance level showed that during the observational follow-up study, the degrading effect was not registered in any child who was administered proteflazid preparations. Against the background of two courses of seasonal prevention with Imunoflazid® syrup or Proteflazid® drops, a significant improvement was recorded in 35.2% of all observations, additionally, positive changes were observed for 2-3 years.

2. Implementation of preventive measures in school- and preschool-aged children using plant preparations Imunoflazid® and Proteflazid® allow reducing by 2 days of ARVI duration on average and 1.7-fold reduction of ARVI incidence in the year, accompanied with a milder course of those cases of ARVI, which failed to prevent.

3. The preventive use of bioflavonoids in the form of Imunoflazid® syrup and Proteflazid® drops restored the bacterial eubiosis of the upper respiratory tract mucosa: the number of children with eubiosis condition doubled.

4. The preventive efficacy of ARVI in children aged from 4 to 9 years with Imunoflazid® syrup and in children aged from 9 to 17 years with Proteflazid® drops made up 82% and is characte¬rised by favourable tolerability, which indicates the high safety of these preparations.

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