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Correction of metabolic disturbances and energy deficiency in children with Bronchial Asthma and Dysfunction of Cardiovascular system

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Abstract

Based on a comprehensive survey of 73 children who suffer from bronchial asthma, in which revealed dysfunction of the cardiovascular system, which were shown by violation of processes repolarization, sinus brady- and tachycardia, incomplete blockade of right bundle of His (IBRB). In biochemical studies arranged the activation of lipid peroxidation (LPO), increased oxidative modification of proteins (OMP), decline in antioxidant protection, the level of ATP and pyruvate, lactate increase. Inclusion in the complex therapy drugs "Cardonat" and "Pikovit Plus" helps to improve function of the main parameters of the cardiovascular system, promotes normalization of antioxidant and energy metabolism.

Keywords: bronchial asthma, children, metabolism, energy deficiency, treatment.

1. Introduction

Bronchial asthma (BA) is the most common chronic respiratory diseases in children, and its incidence is steadily increasing every year in all countries, regardless of their level of economic development [1-3]. Costs, associated only with the treatment of asthma in developed countries account for 1-2% of the total health care institutions budget [1, 3-4]. Despite the availability of effective asthma medications, in many patients asthma control remains suboptimal [2, 4-5]. All the above suggests, that asthma in children is a serious problem of social and medical importance [1, 5-6, 7]. Even with the use of modern combined drugs of basic therapy (budesonide/formoterol and salmeterol/fluticasone) sooner or later in children developing exacerbation of the disease, sometimes - moderate, and sometimes those that require hospitalization, particularly in intensive care units of hospitals [4, 6-7].

In recent years clarified some pathogenic mechanisms of metabolic disorders in asthma, which reduces the effectiveness of the basic sequential therapy. It is established, that free radicals, which formed excessively in oxidative stress, in the airways may participate in the development of bronchospasm during exacerbation of asthma [8-10]. This, in turn, leads to increased permeability of biological membranes due to changes in the structure of proteins and lipids and activation of lipid peroxidation [8, 11-12].

Metabolic disorders and energy deficiency, that develops as a result of these disorders, cause dysfunction of other organs and systems, especially the cardiovascular [9]. Therefore, in recent years is growing interest in metabolic therapy, including the use of endogenous regulators of energy metabolism, that activate their own bioenergetic processes of cells, directing them through natural physiological way [13-14]. They reduce the activity of radical initiating reactions and coordinate response of the Krebs cycle. It is believed, that such means are carnitine containing medications, vitamins and minerals [14-15]. Established, that one of the main vital function of carnitine is bioenergetic [16-17]. Carnitine directly involved in lipid metabolism, that is reserve source of ATP synthesis in the body. Carnitine deficiency, especially in children, in which endogenous reserves are limited, quickly formed, and quickly exhausted in various stressful situations (infections, violation feeding, hypoxic-ischemic CNS lesions, etc.) [15-17]. An interesting and promising metabolic poly protector is Ukrainian preparation Cardonat, which is unique on the composition [15, 18]. Cardonat is a combined carnitine containing drug, effect of which is due constituent parts. Its structure, in addition to carnitine, include: kobamamyd (coenzyme B12); cocarboxylase (vitamin B₁ coenzyme); piridoksal-5-phosphate (coenzyme vitamin B₆); lysine hydrochloride (amino acid, that is involved in all processes of growth and development, stimulates cell division). The advantage of the drug is that it can be used in children from the first year of life. Proved energy-tropic effect of vitamins and

vitamin-mineral complexes in healthy children and in various pathological conditions in children [14, 15]. High prevalence of hypovitaminosis in children, high intensity of metabolic processes, caused by intense growth and energy deficiency against the background of many intercurrent diseases necessitates the use of vitamins and microelements in children. The aim of this study was to evaluate the effectiveness of the use of energy-tropic complex metabolic drug "Cardonat" and vitamin - mineral complex "Pikovit Plus" in children with bronchial asthma and violations of the cardiovascular system functions.

2. Materials and Methods

Carried out examination of 73 children aged 5 to 15 years with asthma and functional disorders of the cardiovascular system, most of which were school-age children (83.6%). Carried out comparative evaluation treatment outcomes of children, who received Cardonat and Pikovit Plus and with traditional treatment. For this purpose the children were divided into 2 groups. The main group consisted of 40 patients, who received in the complex treatment Cardonat and Pikovit Plus, the comparative group consisted of 33 children, who received only basic therapy. The control group consisted of 20 healthy children of the same age. Basic treatment of asthma conducted according to the order of Health Ministry of Ukraine № 767 and GINA-2011 recommendations. The level of asthma control was scored by ACT- test. Groups of children were randomized by age, sex, duration and course of the disease.

All patients underwent general clinical, immunological and instrumental investigations (ECG, heart ultrasound, computer spirometry, peak flow metry) in the dynamics of the disease. Allergic research included study of allergic history, allergy skin testing (prick-tests) with standard sets of allergens ("Sevafarma", Czech Republic). Determination of total IgE was performed by the IFA method with a set of reagents ("Vector-Best", Russia). Allergy diagnostics with a wide range of allergens was performed in vitro using multiple allergic sorbent chemiluminescence test (MAST CLA, Hitachi Chemical Diagnostics), which is the semi-quantitative determination in vitro concentrations of a wide range of allergen-specific IgE and IgG. Lipid peroxidation (LPO) in children with asthma was evaluated on the content of diene conjugates (DC) and thiobarbituric acid active products (TBA-AP), methodology of TN Fedorova *et al.*, 1983. Antioxidant Protection (AOP) was determined by the activity of ceruloplasmin (ACP), the content of glutathione peroxidase (GP) and glutathione reductase (GR) by spectrophotometric method. The activity of lactate dehydrogenase (LDH) was studied using standard sets of test systems (Lachema, Czech Republic). The level of energy metabolism metabolites was evaluated by determining the concentration of serum pyruvate (colorimetric method), lactate (method of Buchner), ATP (by Lamprecht and Trotshold). Statistical analysis of the research results carried out by the software AtteStat Microsoft Excel 2007. Used the method of descriptive statistics of the estimated average indicator values (M), standard error of the mean (m), t-Student's t test. Reliability of superiority of one over the other signs was evaluated using odds ratio (OR) and criterion χ^2 .

2.1. Compliance with bioethics

The survey was carried out in parallel clinical comparison groups, formed on the basis of a simple randomization by the "case-control" method with a strict observance of the bioethical requirements (GCP, ICH and the Helsinki Declaration of the

World Medical Association on biomedical research, in which a person acts as its object, as well as the order of the Health Ministry of Ukraine № 960 of 23.09.2009).

3. Results and Discussions

In the 58 examined children diagnosed BA of moderate severity, in 15 - severe. In allergy test by the method MAST CLA found, that in 54.2% of children with asthma was allergy to tree pollen and grass, in 50% - to house dust, in 45.8% installed epidermal allergy, in 29.2% - for food allergens. Most often *met* allergy to mites *Dermatophagoides pteronissinus* (in 66.6% of children) and *Dermatophagoides farinae* (58.3% in children). In 37.5% of children diagnosed multiple allergy - a combination of home, food allergies and pollinosis.

Clinical manifestations of cardiovascular system dysfunction in children with BA were complaints of fatigue and reduced working capacity (82.4%), discomfort and recurrent pain in the heart area (59.6%), palpitations (26.9%), disruptions of the heart (55.7%). In 86.7% of the patients established ECG changes, from which most often were hypoxia of myocardium, sinus bradycardia, tachycardia, diffuse changes in the myocardium with impaired repolarization processes, beats , violation of intraventricular conduction. When echocardiography in 62.8% patients detected changes of heart in the form of small structural abnormalities (mitral valve prolapse - in 23.9%, abnormal chordae - in 19.7%). Most often in children with BA were observed disturbance of repolarization, sinus brady- and tachycardia, incomplete branch block of right bundle. In 8.9% of children with BA was reduced ejection fraction. Assessment of autonomic homeostasis was carried out using cardiointervalography, that spent in all children. Analysis of the original vegetative tonus showed, that in 45.3% patients domination of parasympathetic system tone observed, in 21.8% - dominated the tone of the sympathetic division of the autonomic nervous system and only in 32.9% patients was determined normal tonus.

Found, that children of both groups in attack term of BA observed intensification of lipid peroxidation processes in blood serum. Evidence of this is increasing content of primary and secondary products of lipid peroxidation. The content of TBA-active products increased to 6.86 ± 0.26 nmol / ml in children of the main group and 6.97 ± 0.19 nmol / ml in children of comparison group, in healthy children this value was 3.76 ± 0.28 nmol / ml ($P < 0.001$). The level of diene conjugates was 2.5 times higher compared with the children in the control group (Table 1).

Process of lipids hyper peroxidation plays an important role in the pathogenesis of inflammatory diseases of different localization, because these processes are crucial in violation of the stability of biological membranes, metabolic disorders and the energy deficiency development.

To evaluate the antioxidant protection investigated enzyme activity of glutathione block (glutathione peroxidase and glutathione reductase), which are essential elements of the antioxidant system, and copper-containing antioxidant enzyme ceruloplasmin. In attack period of illness in children with BA ceruloplasmin activity increased compared with healthy children ($27,82 \pm 1,56$ units) to $41,32 \pm 2,45$ units ($P < 0,001$) in children of the main group and $48,12 \pm 2,22$ units - in children of the comparison group ($P < 0,001$).

Taking into account, that ceruloplasmin has the ability to bind free radicals and allergy mediators serotonin and histamine, we can assume, that its increase in children with BA in dynamics of disease associated with adaptive-compensatory reactions. In

addition, ceruloplasmin belongs to the "acute phase proteins" of inflammation and we can assume, that increasing of it is also

associated with the accumulation of allergic inflammation mediator.

Table 1: Indicators of oxidant-antioxidant status and metabolites of energy metabolism in children with bronchial asthma in attack period (M ± m)

Indicators	Healthy children (n - 20)	Main group (n - 40)	P ₁	Comparison group (n -33)	P ₂
TBA-AP, mmol / ml	3,16±0,28	6,86±0,26	< 0,001	6,97±0,19	< 0,001
DC, conv. units	1,56±0,11	3,86±0,18	< 0,001	3,80±0,15	< 0,001
ACP, conv. units	23,76±0,39	41,32±2,45	< 0,001	48,12±2,22	< 0,001
GR, mkmol / min	0,161±0,008	0,115±0,006	< 0,001	0,110±0,005	< 0,001
GP, nmol / min	0,19±0,02	0,13±0,01	< 0,01	0,12±0,02	< 0,01
LDH, mmol / l	0,152±0,025	0,311±0,016	< 0,001	0,334±0,019	< 0,001
Pyruvate, mkmol / l	14,87±0,25	10,53±0,13	< 0,001	10,68±0,11	< 0,001
Lactate, mmol / l	0,152±0,025	0,311±0,016	< 0,001	0,334±0,019	< 0,001

Note: P₁, P₂ – Student's criterion between parameters in healthy and sick children with asthma.

Protective role of glutathione peroxidase and glutathione reductase in oxidative stress is that glutathione peroxidase carries hydrogen to the oxidized glutathione and glutathione reductase - removes hydrogen and transmits it to H₂O₂, resulting in the formation of two molecules of water. As shown in Table 1, the signs of AOP mechanisms in children with asthma are a significant decline in the activity of glutathione peroxidase and glutathione reductase compared with values in healthy children.

To assess the level of energy metabolism was determined concentration of basic macroergic ATP compound, pyruvate and lactate in the blood serum. It was established, that the level of ATP in sick children (0,393 ± 0,11 mmol/l) decreased by almost half compared with healthy children (0,611 ± 0,07 mmol/l, p <0,001), pyruvate content was reduced to 11,53 ± 0,14 mmol/l (in healthy children 14,87 ± 0,47 mmol/l, p <0,05). However, the level of lactate (0,311 ± 0,16 mmol/l) increased by 2 times compared with healthy children (0,152±0,025, p <0,001). We detected biochemical disturbances, that indicates a compensatory strengthening of anaerobic glycolysis in hypoxia, which occurs in examined children. The high concentration of lactate in the blood of patients indicates developing lactic acidosis and violation of the body energy supply, which reduces the amount of ATP in all children.

In attack term BA significant difference in all parameters of studied children between the main group and the comparison group is not installed.

The obtained data indicate the feasibility of metabolic disturbances correction in children with asthma. We chose energy and metabolic action drugs "Cardonat" ("Sperko Ukraine") and "Pikovit Plus" (KRKA, Slovenia). Cardonat is a combined drug, its energy effect is due to content of carnitine and other parts. The drug helps to normalize the disturbed metabolism, provides a protective effect on the heart, liver, nervous system, reduces ischemia of the heart muscle, activates the metabolism of proteins, carbohydrates and lipids. In particular, L-carnitine (vitamin of growth) plays an important

role in cellular metabolism, converting fat into energy, has the ability to bind with fatty acids in the cells and transport them into the mitochondria for oxidation, reduces signs of physical and mental stress, improves performance^[3, 7]. The endogenous synthesis of L-carnitine in adults provides only 10% of the body's need carnitine. For its synthesis in the organism are necessary vitamins C, B₃, B₆, folic acid, iron, some amino acids and enzymes. In children endogenous synthesis of carnitine is reduced because its deficiency in infancy due to the lack of exogenous admission develops more frequently. Cardonat administered 1 capsule 2 times a day, the treatment lasted 3-4 weeks.

The structure of polyvitamin complex "Pikovit Plus" includes a wide range of vitamins (Retinol, Cholecalciferol, Tocopherol, Thiamine, Riboflavin, Pyridoxine, Cyanokobalamin, Niacin, Ascorbic acid, Pantothenic and Folic acids, Biotin). Moreover, it contains Calcium, Iron, Zinc and, that is very important for the Carpathians region, containing Iodine (in 1 tablet 40 mg of Iodine). "Pikovit Plus" administered 1 tablet 1 time a day for 1 month, course of treatment was repeated in the fall and spring seasons.

Our data suggest a positive clinical and biochemical dynamics in children with BA receiving energy-tropic therapy (Table 2). As shown in Table 2, in the dynamics of the disease under influence of the basic treatment was observed only some tendency to normalization of individual indicators (increased diene conjugates and pyruvate, decreased activity of ceruloplasmin). However, complex use of drugs "Cardonat" and "Pikovit Plus" helps reduction of free radical processes, significantly improves indicators of antioxidant protection and products of energy metabolism.

In 72,7% of children during treatment observed significant improvement of health, a significant decrease in the frequency of attacks of pain in the heart, fatigue, headache compared with a group of children, who received only basic therapy. In 78,8% of children marked on the ECG improvement of metabolic processes in the myocardium, including improving processes repolarization and conduction.

Table 2: The evolution of the oxidant-antioxidant status and metabolites of energy metabolism in children with bronchial asthma, influenced energy-tropic therapy (M ± m)

Indicators	Basic therapy (n - 33)		Basic + energotropic therapy (n - 40)	
	Attack term	After treatment	Attack term	After treatment
TBA-AP, mmol / ml	6,86±0,26	5,82±0,21	6,97±0,19	4,36±0,16***
DC, conv. units	3,86±0,18	3,24±0,14*	3,82±0,18	2,15±0,14***
ACP, conv. units	41,32±2,45	42,53±1,93*	48,12±2,22	31,55±1,59***
GR, mkmol / min	0,112±0,004	0,131±0,002	0,125±0,013	0,178±0,012**
GP, nmol / min	0,13±0,04	0,15±0,06	0,12±0,02	0,21±0,03***
ATP, mmol / l	0,393±0,015	0,433±0,021	0,388±0,028	0,515±0,032**
Lactate, mmol / l	0,311±0,016	0,273±0,021	0,334±0,019	0,191±0,018***
Pyruvate, mkmol / l	10,53±0,13	12,62±0,12*	10,68±0,11	14,13±0,13***

Notes: 1. P – Student's criterion in children under the influence of treatment.
2. * - P < 0,05; ** - P < 0,02; *** - P < 0,001.

4. Conclusions

Objective criteria for improving the quality of life in children with BA with impaired function of the cardiovascular system, obtaining complex preparations "Cardonat" and "Pikovit Plus" have been reducing the frequency of medical emergencies and hospitalization, improvement working capacity and reducing the number of missed days at school because of the disease. Under the influence of metabolic and energy-tropic therapy showed a significant reduction in the primary and secondary products of lipid peroxidation, increased activity of antioxidant enzymes, ATP content and normalization of energy metabolism products compared with children, who received only basic therapy.

About efficiency and preference of inclusion metabolic and energy-tropic preparations in complex treatment of children with asthma compared with traditional methods of basic therapy shows high odds ratio and confidence intervals (OR = 9,3333; CI = 2,9157- 29,8761) and high reliability in χ^2 criteria (P < 0,00019).

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