UDC 615.23:612.015.11:546.172.6

SYRUP AMKESOL REDUCES THE LEVEL OF PRIMARY AND SECONDARY PRODUCTS OF LIPID PEROXIDATION AND TOXIC METABOLITES OF NITRIC OXIDE IN BLOOD SERUM OF IMMATURE RATS WITH BRONCHIOLITIS

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Introduction

Broncho-pulmonary diseases are the most common childhood disorder [1] . In fact, 25-31% of children's respiratory infections lead to clinical manifestations of obstructive bronchitis, and in 30-50% of cases are having prolonged, undulate or recurrent course [2, 3]. Furthermore, recurrent obstructive bronchitis in children is considered to be a manifestation of bronchial asthma [4].

The alteration in the lipid peroxidation - antioxidant protection (POL-AO) system and rising of nitric oxide are known to be essential in the development of bronchopulmonary pathology [5]. Basically, the major pathogenetic factor of bronchopulmonary pathology is chronic or acute inflammation, which clinically is manifested by swelling, hypersecretion, constriction of bronchi and hypoxia [6]. Obviously, inflammatory process induces “respiratory burst", that characterized by imbalance between lipid peroxidation and AO protection and accompanied by rising of NO [7]. In fact, it's allows to interpret the concentration of nitrates and N-nitro compounds in blood serum as a marker of acute nonspecific inflammatory process [8]. Thereby, reduction of primary and secondary products of lipid peroxidation and NO toxic metabolites and restoration of AO enzymes activity in inflammatory respiratory diseases have clinical significance and can be used as additional criteria to determine effectiveness of the therapy [9].

Besides, pathophisiologycal reactions of upper respiratory tract caused by infectious inflammatory process are age-depended due to anatomical and physiological characteristics of child's body. Therefore taking them into account is essential for the treatment of children with respiratory diseases [10]. For instance, one of the physiological responses of the first three years of life children is a sustain hyperproduction of highly-viscous mucus in combination with edema of bronchial mucosa, that subsequently violates second mucociliary transport, causes bronchial obstruction and promotes infectious inflammation [11]. Additionally, immune system of 2-6-years-old children is characterized by excessive proliferative activity of lymphocytes and higher levels of cell-mediated cytotoxicity compared with adults. Such phenomenon usually causes high sensitivity to infections and less specific response of the immune system. Moreover, for infants and children, the immune response to infectious antigens is predominantly Th2-response while in adults it is usually Th1-response [12].

Nowadays, comprehensive treatment of respiratory disease must include anti-inflammatory drugs along with conventional antimicrobial and symptomatic therapy. Apparently, the advantages of rational composition of combined medicines in the treatment of broncho-pulmonary diseases are they synergistic action on the pathogenesis, decreasing of the risk of side effects, and in finally avoidance of unintended interactions of individual drugs. As such this results in prevention of polypharmacy that is particularly important for functional immaturity of children’s organs and systems [13]. The problem of developing children's dosage forms, among which the oral solutions and syrups are most preferred, gains particular attention [14].

One of the recent combined preparation that recommended for the treatment of broncho-pulmonary diseases in Ukrainian pharmaceutical market is tablets Amkesol that manufactured by CPP "Chervona zirka", PJSC, Kharkiv, Ukraine [15]. According to the current needs of the Ukrainian pharmaceutical market to have an effective and safe pediatric medicine, it is important to develop and explore a child dosage form for Amkesol.

The aim of this study was to determine the pharmacological effect of syrup Amkesol (S-AKS) (Ambroxol, ketotifen, licorice root extract) as a children analogue of tablets Amkesol evaluating the blood serum levels of primary and secondary products of lipid peroxidation, activity of AO enzymes and final rates of NO metabolites in immature rats of different ages with experimental model of bronchoalveolitis.

Material & methods

The study was carried out on 90 WAG immature rats of ages 1, 2 and 3 monthes, that correlats by morpho-functional features to 4, 10 and 14 years of human age respectively [16]. Animals were kept in standard condition of experimental biological clinic KhNMU, by 5-6 animals in the cage 60 × 60 × 60 cm, air temperature - 20-25º C. Experiments were conducted in accordance with the protocol of the Ukrainian Association of Bioethics (1992) the directive of the European Convention for the protection of vertebrate animals and the European economic Society for the protection of vertebrate animals (Strasbourg, 1986) and approved by KhNMU ethics committee. Experimental animals in each age series were randomly divided into 5 groups (n = 6): intact (healthy), 2 groups of control (untreated with bronchoalveolitis) 7 and 14 days, and two groups with bronchoalveolatis that received S-AKS daily during 7 and 14 days .

The model of bronchoalveolitis in rats [17] used to provide an inflammation with allergic component that is localized in the lung tissue. Reproduction of the pathological process implemented by inhalation of irritant (Sephadex A-25, Pharmacia, Sweden, 5 mg / kg) in the upper airways of animals using an ultrasonic nebulizer for dry medications [18] via subclavian catheter 1.0 mm, with the further development of aseptic inflammation and involvement of immune mechanisms.

To the powder fell into trachea and bronchi, rats in anesthesia were fixed by cutters of upper jaw and pulled by lower jaw with the tongue using ligature. At the time of inhalation wings of the animal nose were pressed to the membrane with two fingers.

Development of experimental inflammation was studied in the dynamics on 7 and 14 days after inhalation exposure of Sephadex A-25. S-AKS was administered intragastrically using a metal probe with a rounded end. The daily dose was calculated based on the coefficient of species sensitivity in rats [19] (respectively for human dose) and amounted to 0.9 ml / kg of body weight. Anti-inflammatory effect of S-AKC was evaluated by studying concentration of products of POL, activity of AO enzymes, level of NO-metabolites in the blood serum, which is objectively, responds to inflammation. Blood serum was collected after euthanasia by decapitation with anesthesia (Thiopental sodium 60 mg / kg intraperitoneally). Blood was obtain from the carotid artery in a clean dry test tube, allowed to clot for 30 min at room temperature, and centrifuged at 1000-1500 G for 15 min to get serum. Serum aliquots were stored at -90 C until biochemical analyses.

Condition of POL was measured by the amount of primary active products of lipid peroxidation - diene conjugation (DC) and intermediate - Thiobarbituric acid–reactive substances (TBARS), the functioning of AOC - by activity of key antioxidant enzymes - catalase (CAT) and superoxide dismutase (SOD).

Determination of DC conducted by spectrophotometry at the wave length 233 nm (versus ethanol) [20].TBARS was measured by modified fluorometric method using reaction with tiobarbituric acid [21]. CAT activity was determined by the method [22] based on the hydrogen peroxide ability to form stable colored complex with salts of molybdenum. SOD activity was measured by reaction of quercetin oxidation in modification of V.A.Kostyuk [23].

For the more objective evaluation of the POL-AO system reactivity integral coefficient of AO protection (IC) was calculated as follows:

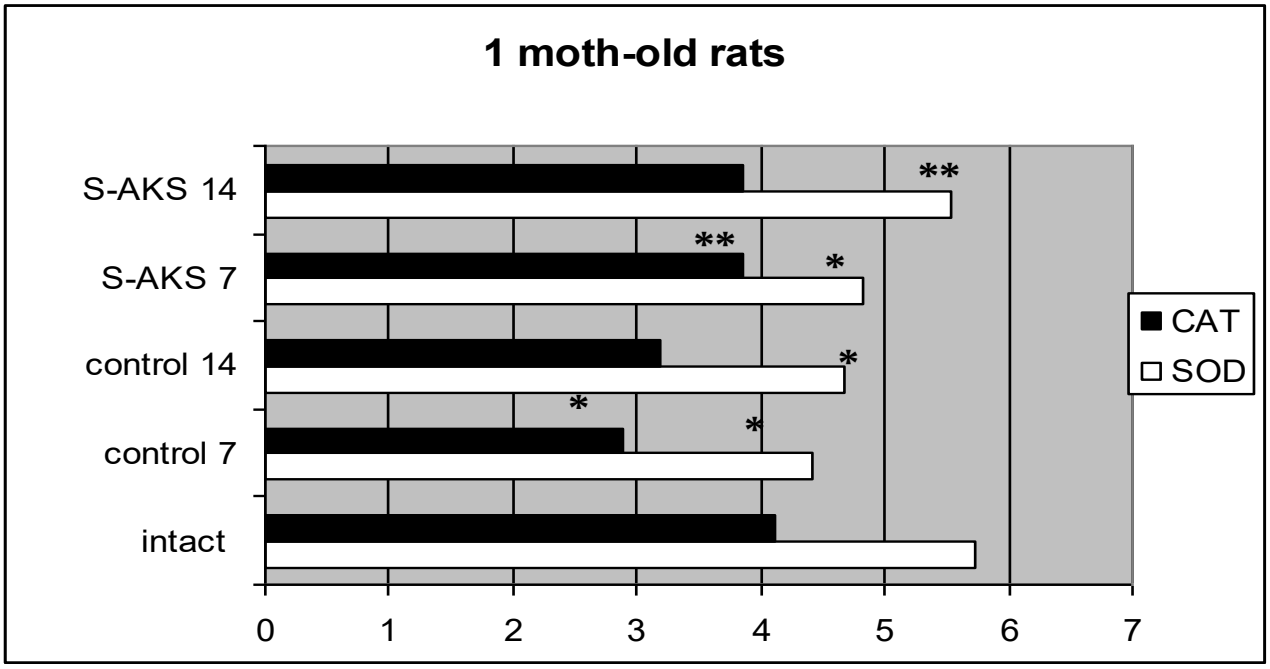
$$IC=\frac{SOD\times CAT}{TBARS},$$

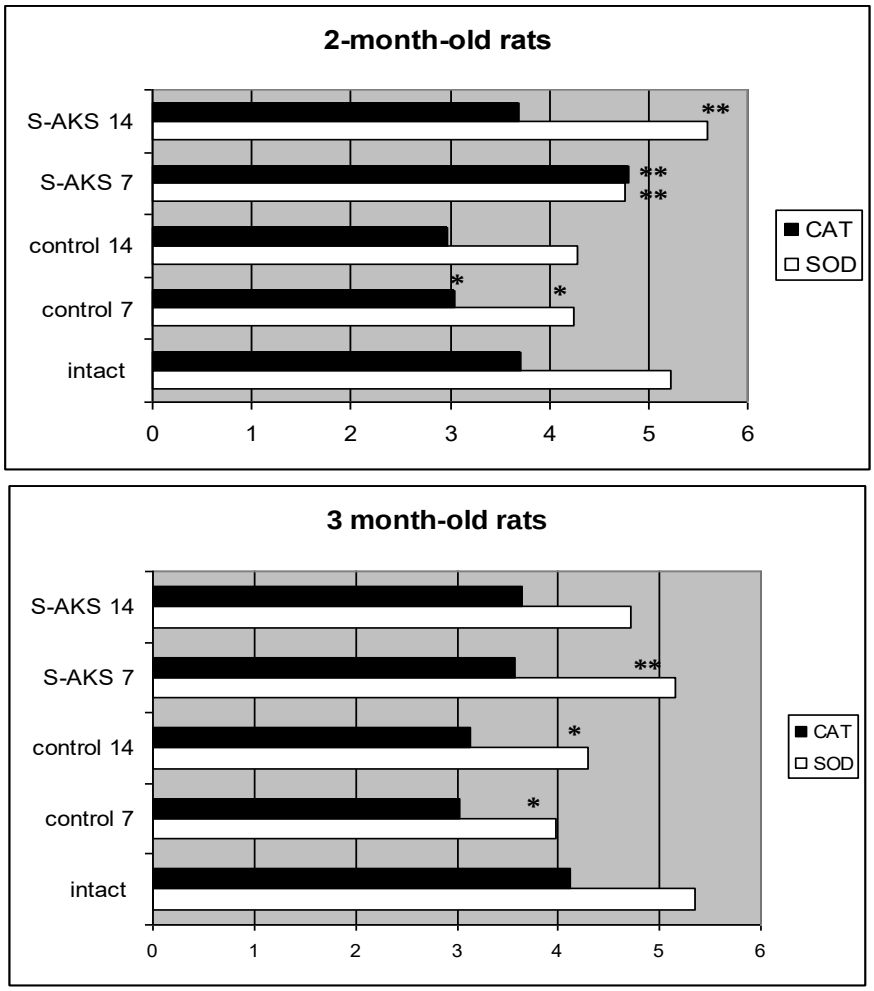
where SOD - an indicator of the activity of superoxide dismutase, CAT is catalase activity, TBARS -level of Thiobarbituric acid–reactive substances in relevant group of animals [24].

The contents of total NO, nitrates and nitrites were determined by spectrophotometric method on a spectrophotometer SF-4A [25] by reduction of nitrate to nitrite with granules of cadmium.

Probability of the results was evaluated by using Student t-test and U-Mann-Whitney (GraphPad Prism Software) [26]. The critical level of significance was taken equal to 0.05.

Results & discussion After 7 days in acute neutrophilic alveolitis in 1- and 2-month-old rats of the control group (no treatment) activity of SOD and CAT decreased significantly ($P\leq0,05$) compared to intact animals of the same age. At the same time, in the group of 3-month-old rats SOD activity was significantly decreased only ($P\leq0,05$) (Fig.1).





** - P <0.05 v.s. intact group*

*** - P <0.05 relative to the control group with the corresponding period of experimental inflammation*

Fig.1. Effect of syrup Amkesol on the Antioxidative Enzyme Activities in serum of immature rats with bronchoalveolitis (U/mg protein)

After 14 days in the control group without treatment in all age series inhibition of SOD was observed (P≤0,05) compared to intact animals, significant reduction the level of CAT (P≤0,05) manifested only in 2-month-old rats.

However, due to inflammation the process of lipid peroxidation was significantly activated. On the 7th day in the control group of all age series of experiment DC level was sharply increased compared to the intact group (P≤0,05) (Fig. 2).

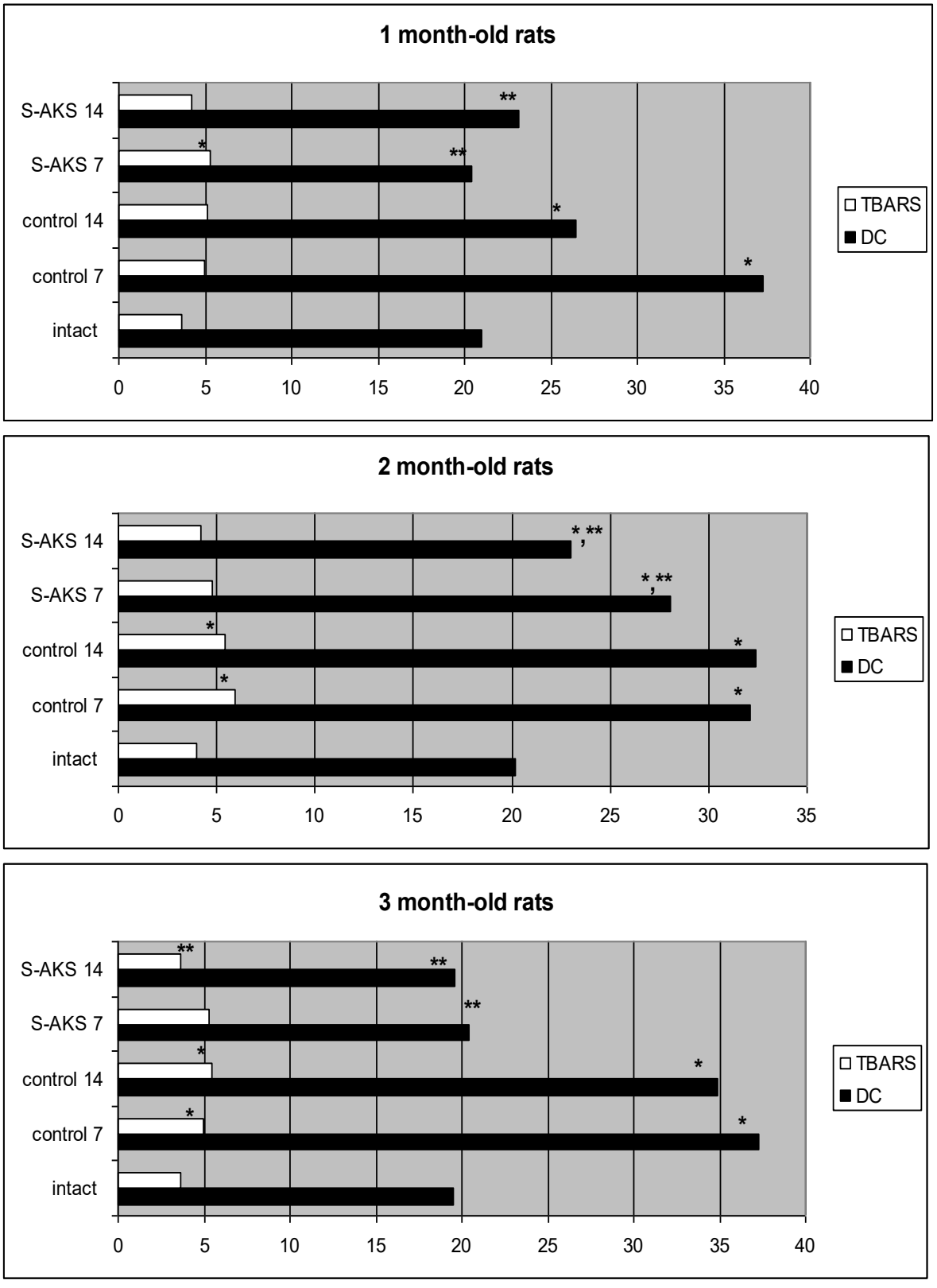
The most expressive increases of DC reached in 3-month-old rats and amounted 191% compared to the intact group. The content of secondary products of lipid peroxidation-TBARS significantly exceeded the indices of age norm in 2- and 3-month-old animals (P≤0,05) and tended to increase in the group of 1-monthly rats.

On the 14th day in the control group of 1 monthly rats level of the DC exceeded the data of intact animals in relevant age group by 26%, in 2 monthly by 60%, in 3 monthly by 79% (P≤0,05). The concentration of TBARS was significantly greater the initial level in all studied age groups of animals (P≤0,05). So in the control group in all age series on the 14th day was marked tendency to rise of secondary products of lipid peroxidation - TBARS compared with results on the 7th day.

Changes of individual parameters of free radical oxidation don't give a holistic view of the oxidative stress severity and tension of AO-defense system. Using research findings, integral coefficient (IC) of AO protection was calculated, which more accurately describe the state of equilibrium processes of peroxidation and AO protection (Table 1).

On the 7th day in the control group of 1-month-old animals IC significantly decreased by 73%, and on the 14th day by 58% (P≤0,05). In the control group of 2-month-old rats on the 7th day IC decreased by 55%, and on the 14th day by 52% (P≤0,05). In the group of 3-monthly animals on the 7th day IC value was 40% and on the 14th day IC amounted 41% from the intact group (P≤0,05).

Thus, reactivity of metabolic balance of antioxidant-prooxidant system due to inflammation is age-dependent. In the group of 1-month-old animals IC were characterized by the highest baseline and largest reactivity in response to inflammation.



* - P <0.05 v.s. intact group
** - P <0.05 relative to the control group with the corresponding period of experimental inflammation

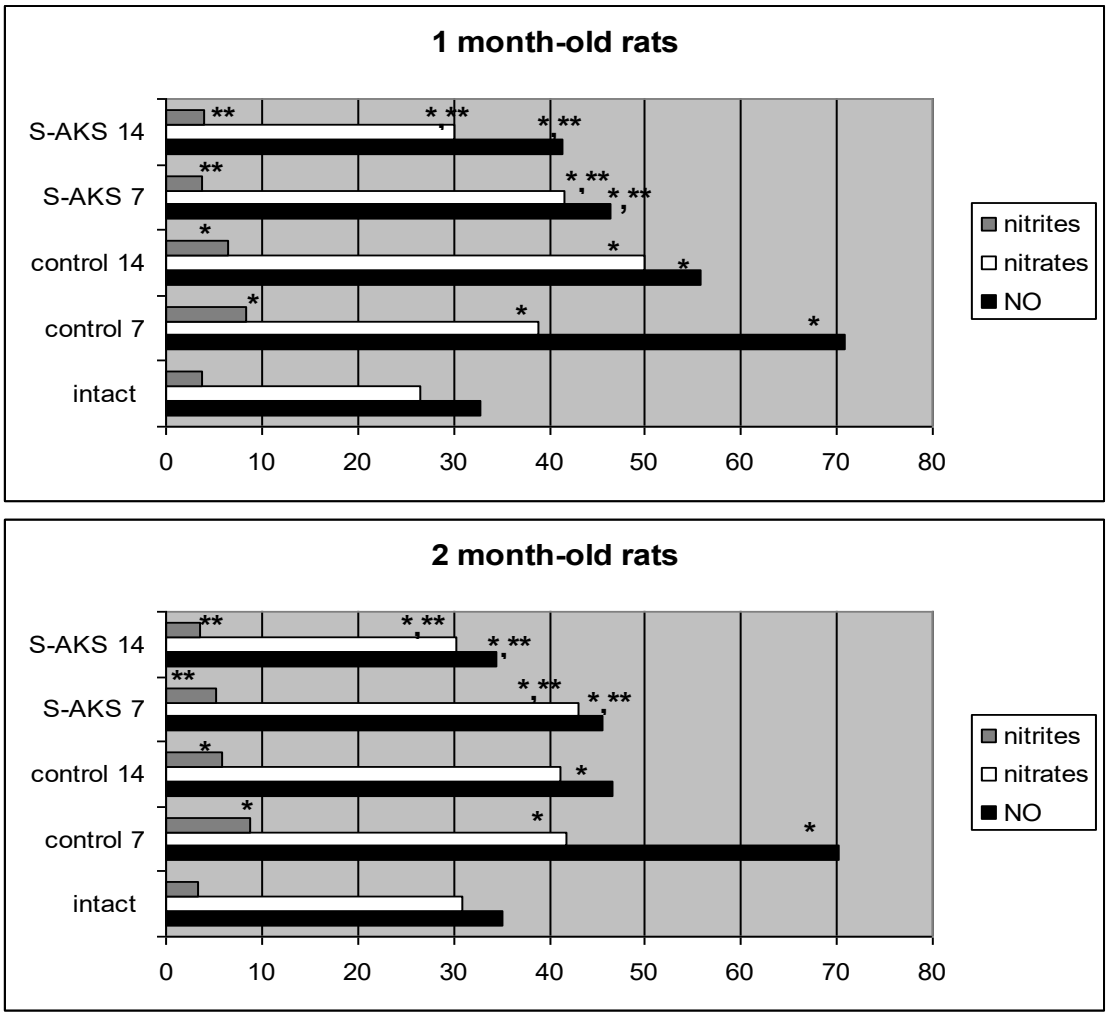
Fig.2. Effect of syrup Amkesol on serum diene conjugation (DC) and thiobarbituric acid-reactive substances (TBARS) of immature rats with bronchoalveolitis ((µmol/mL)

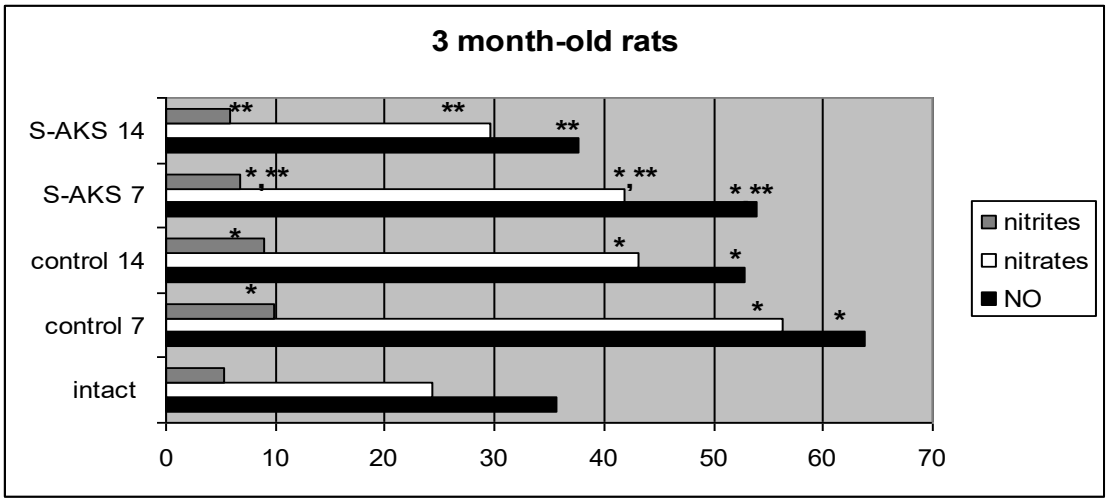
Table 1. Integral coefficient of AO protection in serum of immature rats with bronchoalveolitis and due to effect of syrup Amkesol.

Group / Age	Intact	Control 7 days	Control 14 days	S-AKS 7 days	S-AKS 14 days
1 month	8,4±0,7	2,2±0,5*	3,5±0,41*	3,48±0,53*	5,15±0,73*
2 months	4,91±0,6	2,18±0,53*	2,36±0,68*	4,8±0,62**	4,84±0,7**
3 months	6,07±1,01	2,42±0,44*	2,48±0,47*	3,47±0,25*	4,74±0,85**

* - P <0.05 v.s. intact group; ** - P <0.05 relative to the control group with the corresponding period of experimental inflammation

The contents of total NO metabolites on the 7th day in the control group of 1-month-old rats increased more than twice (Figure 3). In the control group of 2-month-old animals the level of NO metabolites was doubled as compared with corresponding age norms, in the control group of 3-month-old rats amount of the total NO was increased by 79% (P≤0,05).





* - P <0.05 v.s. intact group; ** - P <0.05 relative to the control group with the corresponding period of experimental inflammation

Fig.3. Effect of syrup Amkesol on serum contents of total nitric oxide metabolites of immature rats with bronchoalveolitis ((μmol/mL)

On the 7th day content of nitrites in serum was increased in 2-2.5 times in all age groups (P≤0,05). Rising of nitrates was observed in a much lesser extent – by 46% in 1-month-old animals, by 35% in the 2-monthly and 32.7% in the 3-month-old rats compared with intact animals (P≤0,05) .

After 14 days in the control group of 1-month-old animals the level of total NO remained higher at 70%, the concentration of intermediate and final metabolites of NO accounted 75 and 85% higher than the rates of intact rats respectively (P≤0,05). In the relevant group of 2-month-old rats concentration of NO metabolites was amounted 132%, nitrates level was 133.5% and nitrites level was 170% compared to the intact group. In 3-monthly rats was observed increase of total NO by 48%, the level of nitrates increased by 77% and amount of nitrites raised by 72% (P≤0,05).

According to received data, by the 7th day experimental bronchoalveolitis caused significantly increased level of lipid peroxidation products and suppressed activity of AO enzymes in animals of all studied age groups. The level of nitric oxide metabolites was increased almost twice, that indicated development of acute inflammation. On the 14th day indicators of POL displayed slight decreasing of oxidative stress and activation AOS enzymes, apparently due to adaptive and compensatory mechanisms in the background of chronic inflammation. The concentration of stable NO metabolites remained significantly high, which is consistent with the dual role of NO in the POL. On the one hand, it has the properties of free radicals and is involved in the oxidation and nitrification that form the base of POL, on the other hand - is able to inhibit lipid peroxidation intensity and activate the AO system [27].

The use of S-AKS reduced severity of lipid peroxidation and increased activity of AO enzymes in blood serum in both terms of inflammatory process compared to the control group of animals of all studied age groups.

Thus, by the 7th day in group of 1 month-old rats, that received S-AKS, SOD and CAT activity were significantly higher than the control group value with the corresponding period of inflammation (P≤0,05) (Fig 1). The SOD activity in group of 2-month-old animals was restored to 91%, the activity of CAT exceeded the baseline level and amounted to 129% (P≤0,05). In 3 monthly animals the SOD activity was 96% and exceeded value of the control group (P≤0,05).

By the 14th day activity of AO enzymes in 1- and 2-month-old experimental groups of animals reached data of age norms and values was significantly higher than levels in the control group (P≤0,05). Treatment with S-AKS restored SOD and CAT activity by 88% from the intact animals in the group of 3 months-old rats.

On the 7th day in experimental group of 1 month-old rats the level of DC was 77% lower comparing to the relevant control group (P≤0,05) (Fig. 2). The concentration of TBARS exceeded the intact level by 46%. In the group of 2-month-old animals on the 7th day using of S-AKS increased the level of DC compared to the intact group and significantly reduced relative to control values (P≤0,05), the concentration of TBARS remains higher than the level of the intact group. In the group of 3-monthly rats content of primary lipid peroxidation products on the 7th day reached an intact level, the level of TBARS remained higher of the index of age norm.

After 14 days of treatment with S-AKS in all age group of animals observed restore the contents of primary and secondary products of lipid peroxidation compared to the intact level.

Analysis of IC showed that the most expressive restore of metabolic balance observed in the group of 2-month-old rats: on the 7th day of treatment with S-AKS it was 97.8% and on the 14th day reached 98.5% (P≤0,05). The lowest restoration of the metabolic status was in the group of 1-month-old animals: on the 14th day of treatment with S-AKS IC amounted 61% to the value of intact group (P≤0,05) (Table 1). Thus, the greatest

degree of IC restoration for 14-day use of the S-AKS up to physiological level observed in the group of 2-month-old animals. The lowest rate of IC recovery on the 14th day was in 1-month-old rats group.

The level of NO metabolites on the 7th day of use S-AKS significantly decreased compared to the corresponding control group in all age series ($P \leq 0,05$) (Fig. 3). The rate of nitrate exceeded value of intact animals, but significantly decreased relative to the corresponding control group in all age series ($P \leq 0,05$). Concentration of nitrites in 1-month-old rats reached intact values ($P \leq 0,05$). In the group of 2-month-old animals nitrites level remained higher by 54% relative to baseline data, in 3-monthly animals concentration of nitrites was elevated by 30% compared to intact group. On the 7th day in all studied age groups the concentration of nitrites was significantly lower to the control group ($P \leq 0,05$).

The use of S-AKS within 14 days restored level of total NO and its stable metabolites in the serum of experimental animals all studied age groups.

According to received data, the experimental inflammation caused marked activation of peroxidation and nitrification processes. The increase in lipid peroxidation was associated with decreased activity of AO enzymes. Use of S-AKS in 1-, 2- and 3-month-old rats restored activity of SOD and CAT, lowered the level of primary and secondary products of lipid peroxidation and toxic metabolites of NO in blood serum of all age grade. The marked age differences in the dynamics of biochemical parameters in experimental inflammation and by the effect of S-AKS can be explained, apparently, by anatomical and physiological peculiarity of immature animals. Thus, toddlers, children and adolescents have substantial differences not only in reactivity, immune system, cholinergic activity and secretory function of upper airways, but in pharmacokinetic aspects: ontogeny of hepatic cytochrome P450, plasma protein binding, renal function, development of first-pass gut metabolism. Some *in silico* methods such as Simcyp® Paediatric model allow the prediction of steady-state dosage in children to replicate net systemic drug exposure in adults, but are not intended to replace clinical trials [28].

Conclusion

1. Administration of S-AKS (0.9 ml /kg) daily within 7 days in 1-, 2- and 3-month-old rats with bronchoalveolitis reduced level of primary products of lipid peroxidation; caused significant increase of CAT and SOD activity; significantly decreased the total concentration of NO, and lowered the content of nitrite anion average 2-fold relative to the control group on the 7th day. The concentration of TBARS in all treatment groups on the 7^{th} day remained significantly elevated relatively to the values of age norms.

2. Administration of S-AKS (0.9 ml / kg) daily within 14 days in 1-, 2- and 3-month-old rats with bronchoalveolitis reduced the values of primary and secondary products of lipid peroxidation ; restored the activity of antioxidant enzymes; reduced the level of NO and its stable metabolites to the physiological level.

3. Antioxidant protection integral coefficient dynamics influenced by inflammation has age differences. The index of IC in 1-month-old animals that for anatomical and morphological characteristics correspond to 4 years of man has had the largest output, the highest reactivity in response to acute inflammation, and the lowest measure of recovery with use of S-AKS. The index of IC in 2 months-old animals, that corresponded to prepubertal period of man life, with use of S-AKS within 7 and 14 day has restored to the intact level.

4. Probably, to eliminate mentioned differences in the dynamics of POL-AO and nitric oxide system data in animals of different age groups, it's required to further study the effect of syrup Amkesol with dose adjustments not only by body weight, but the anatomical and physiological characteristics of animals of different ages.

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Storozhenko K.V.

Aim of this study was to determine the pharmacological effect of syrup Amkesol evaluating the blood serum levels of primary and secondary products of lipid peroxidation, activity of AO enzymes and final rates of NO metabolites in immature rats of different ages with experimental model of bronchoalveolitis. **Materials and Methods:** The study was carried out on 90 WAG immature rats of ages 1, 2 and 3 menthes, that correlates by morpho-functional features to 4, 10 and 14 years of human age respectively, on a model of bronchoalveolitis. Experimental animals in each age series were randomly divided into 5 groups (n = 6): intact (healthy), 2 groups of control (untreated with bronchoalveolitis) 7 and 14 days, and two groups with bronchoalveolatis that received S-AKS daily during 7 and 14 days. The pathological process implemented by inhalation of irritant (Sephadex A-25 Pharmacia, Sweden (5 mg/kg)). In the blood serum samples activity of CAT, SOD, content of DC, TBARS, total NO, nitrates and nitrites were determined. Probability of the results was evaluated by using GraphPad Prism Software. The critical level of significance was taken equal to 0.05. **Results.** The use of S-AKS on the 7th day in the group of 1- and 3-month-old rats significantly exceeded activity of CAT compared to the control group of animals of corresponded age. The SOD activity in group of 2-month-old animals was restored to intact level, the activity of CAT exceeded the baseline level and amounted to 129% ($P \leq 0,05$). The concentration of DC in 1-month-old rats was lower by 45.3% in 2 monthly - by 12.5% than in the control group, in the group of 3 month-old animals - restored to normal ($P \leq 0,05$). The level of NO metabolites was significantly decreased compared to the corresponding control group in all age series ($P \leq 0,05$). After 14 days of treatment with S-AKS in all age group of animals observed restore the contents of primary and secondary products of lipid peroxidation compared to the intact level. **Conclusion.** Administration of S-AKS reduced the values of primary and secondary products of lipid peroxidation; restored the activity of antioxidant enzymes; reduced the level of NO and its stable metabolites to the physiological level in all studied age groups of animals with experimental bronchoalveolitis.
Keywords: children's dosage forms, syrup Amkesol, bronhoalveolitis, prooxidant-antioxidant system, nitric oxide metabolites.