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# WHAT IS THE ROLE OF NUCLEINAT IN A COMPLEX OF CONTROL THERAPY OF BRONCHIAL ASTHMA IN SCHOOL-AGE CHILDREN? DOUBLE-BLIIND PLACEBO CONTROLLED METHOD

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**Abstract.** The effect of Nucleinat on bronchial hyperresponsiveness, the parameters of the phagocytic activity and phagocytic index of neutrophils their oxygen-dependent metabolism and the blood content of nitric oxide metabolites in 98 school age children with bronchial asthma has been studied by means of a double-blind placebo-controlled method. Two clinical groups were formed with the help of the table of accidental numbers. The first clinical group included 47 children who took Nucleinat in a dose of 0,25 g per diem during 21 days in a complex of base-line theraphy. The second clinical group was formed of 51 children who took placebo according to the same regimen. It has been shown that thanks to the use of Nucleinat a reduction of bronchial hypersensitivity and optimization of disease control have been achieved, which was indirectly evidenced by an increased risk of detecting moderate bronchial responsiveness to histamine (OR = 3,6; 95% CI: 1,3-9,3) and a decrease of the phagocytic activity of neutrophils (OR=1,9 with 95% CI (0,9-4,4)).

**Key words:** children, bronchial asthma, bronchial hyperresponsiveness, immunity, Nucleinat.

**Introduction.** Changes of the immune response underlie bronchial asthma (BA). They are the causes of the organism's sensibilization, the development of bronchial allergic (immunologic) inflammation [5] and hyperresponsiveness [7]. Thanks to these inflammatory changes it is very important to use anti-inflammatory drugs for children with bronchial asthma [11]. But, when we use basic therapy this child's pathology, sometimes, it is impossible to attain full control of the diseases [6]. The insufficient effectiveness of the inhalation of glucocorticosteroid (iGCS) [3] substantiates the use of new medications (for example Nucleinat) which can improve BA.

Since Nucleinat possesses immunomodulating and antiinflammatory effects [9], it may be suggested that its use in combined basic therapy in children with bronchial asthma would be accompanied with the positive dynamics of bronchial hyperresponsiveness, the phagocytic activity and the phagocytic index of neutrophils, oxygen-dependent metabolism of neutrophilic granulocytes and the blood content of oxygen.

**The object of the study**: To estimate the role of Nucleinat in the complex of control therapy of children's BA and its effects on bronchial hypersensitivity, the parameters of the phagocytic activity and the phagocytic index of neutrophils, oxygen-dependent metabolism of neutrophilic granulocytes and the blood content of nitric oxide (NO).

**Material and Methods**: Altogether, 98 school-age children with bronchial asthma during the period of remission were subjected to a complex examination. The examinations were performed by means of a double blind, randomized, placebo controlled method. Using the table of random numbers, all the patients were divided into two clinical groups. The first (I) group consisted of 47 patients, who were administered Nucleinat in a dose of 0.25 g/day for 21 days as an addition to combined basic therapy. The second (II) group consisted of 51 patients, who, instead of Nucleinat were administered placebo. The groups did not differ significantly by age, the duration of the disease, the levels of bronchial asthma control or the type of anti-inflammatory therapy.

The first clinical group consisted of 32 boys (68,0 %) and 15 girls (31,9 %). The second clinical group consisted of 31 boys (60,8%, Pφ>0,05) and 20 girls (39,2%, Pφ>0,05).

The average child's age was 11,7±0,5 years in the basic groups and 12,3±0,4 years (P>0,05) in the control group.

According to the classifications of BA, which is in the GINA-2006, there were 5 children (10,6±4,5)% with controlled asthma in the first group and 9 patients (17,6±5,3)% in the second one (P>0,05), 24 children (51,1±7,1)% with partly controlled asthma of group I and 32 (62,7±6,8)% sick children of group II (P>0,05). Uncontrolled bronchial asthma was observed in 18 children (38,3±7,1)% in the first group and in 10 patients (19,6±5,5)% in the second one (P<0,05).

In addition to the generally accepted clinical examinations, the determination of respiratory tract hyperresponsiveness was performed with the use of a portable calibrating spirograph MicroLab (Micro Medical). Bronchial hypersensitivity was estimated by the findings of an inducing dose of histamine, which resulted in a 20% reduction of FEV1 (PC20H), and a cumulative dose (PD20H) with the use of a histamine serial dilution [12]. Bronchial reactivity was determined by means of the bronchial lability index (BLI). A response of the respiratory tracts to a dosed physical exercise (5-min running with a submaximal heart rate) as the bronchospasm index (BSI) and following the inhalation of a $beta_2$-agonist (salbutamol) as the bronchodilation index (BDI) [1]. At the same time, a blood immunological examination of the IInd-IIId levels was performed. In addition to an evaluation of the phagocytic activity (PA, percent) and the phagocytic index (PI, arbitrary units) of blood neutrophils, oxygen-dependent me-

tabolism of neutrophilic granulocytes by the parameters of both spontaneous and stimulated NBT-test, expressed in the form of a relative content (percent) of pharmasan-positive blood neutrophils (V.V. Klimov et al., 1988) was carried out. A determination of blood nitric oxide was also performed (N.L. Yemchenko et al., 1994).

Besides, the risk of the realisation of an event in the first group of children to the patients from the control group (OR with its CI) was calculated.

**Results and Discussion**. Following the therapy carried out in both groups, a reduction in bronchial hypersensitivity was revealed in the form of an elevated inducing and cumulative doses of histamine. However, significant elevations in PC20H and PD20H were only noted in the patients of the first group, while a trend towards elevations of these parameters was noted in the second group patients (Tabl. 1).

The results obtained can be explained by a reduction of the inflammatory component of bronchial hypersensitivity as a result of the therapy instituted [8].

The risk of a reduction of bronchial hypersensitivity in the patients of the first clinical group was higher relative to the children, receiving placebo (OR=3,6; 95 % CI: 1,3-9,3).

Following the therapy, spirographic tests with a dosed physical exercise and with the inhalation of a $beta_2$-agonist showed a trend towards elevations of the bronchial lability index in the patients of both groups (Tabl. 2).

Therefore, a clear trend towards a rise in bronchial sensitivity to $beta_2$-agonist inhalation, but with unchanged bronchospasm as the respiratory tract response to physical exercise was noted in the children receiving Nucleinat. The trend towards enhanced sensitivity of the respiratory tracts to a bronchodilatator, but with the same bronchospasm following a dosed physical exercise in the Nucleinat recipients could be explained by a reduction of the inflammatory component, but with the preserved hereditary component of bronchial reactivity [4].

At the same time, following the therapy in the patients of both clinical groups changes in the oxidation-reduction processes in the blood neutrophilic granulocytes were noted and which were confirmed by the NBT-test findings in both spontaneous and stimulated versions. Thus, significant reductions in the oxygen-dependent bactericidal action of neutrophils were revealed in the children, who received Nucleinat, but only those based on the parameters of the spontaneous NBT-test in the second group patients. An estimation of the relative content of blood neutrophils stimulated with pyrogenal showed a trend towards their reductions in the patients of both clinical groups. An estimation of the functional activity parameters of the phagocytic immunity link showed that Nucleinat in the complex of the basic therapy of children's BA didn't change substantially the phagocytic index and phagocytic activity (Tabl. 3).

Significant reductions in the percentage of pharmasan-positive neutrophils in patients of the first clinical group indicate a plausible reduction of the body's chronic inflammatory process [12].

It is necessary to note, that the probability of a decrease of the phagocytic activity in the patients of the 1st-clinical group relative to the children, receiving placebo was increased (OR=1,9 with 95 % CI (0,9-4,4)).

Following the therapy performed, a significant elevation of the blood nitric oxide content was noted in the first clinical group patients who received Nucleinat (Tabl. 4).

The significant elevated blood nitric oxide content in the first clinical group patients, who received

**Table 1**

**Parameters of respiratory tract hypersensitivity in patients of both clinical groups**

| Group / Therapy | PC20H (mg/ml) | | PD20H (mg) | |
|---|---|---|---|---|
| | I group (n=47) | II group (n=51) | I group (n=47) | II group (n=51) |
| Prior to the therapy | 1,3±0,2 | 1,7±0,3 | 0,29±0,05 | 0,37±0,06 |
| Following the therapy | 2,8±0,5 | 2,2±0,4 | 0,6±0,1 | 0,48±0,1 |
| P | P<0,05 | P>0,05 | P<0,05 | P>0,05 |

**Table 2**

**Parameters of the respiratory tract hyperreactivity in patients of both clinical groups**

| Group / Therapy | Bronchial lability index,% | | Bronchodilation index, % | | Bronchospasm index, % | |
|---|---|---|---|---|---|---|
| | I group (n=32) | II group (n=33) | I group (n=32) | II group (n=33) | I group (n=32) | II group (n=33) |
| Prior to the therapy | 23,4±2,3 | 22,4±2,2 | 9,9±1,4 | 11,3±1,6 | 12,4±1,8 | 11,1±1,2 |
| Following the therapy | 24,6±2,5 | 24,8±3,3 | 11,7±1,6 | 10,8±1,2 | 13,04±1,6 | 14,0±2,7 |
| P | P>0,05 | P>0,05 | P>0,05 | P>0,05 | P>0,05 | P>0,05 |

**Table 3**

**Functional activity parameters of blood neutrophils in patients of both clinical groups**

| Group | NBT-test (%) | | | | FA (%) | | PI (a.u.) | |
|---|---|---|---|---|---|---|---|---|
| | Spontaneous | | Stimulated | | | | | |
| | Prior to therapy | Following therapy | Prior to therapy | Following therapy | Prior to therapy | Following therapy | Prior to therapy | Following therapy |
| I group (n=47) | 36,2±2,5 | 28,0±2,0* | 51,3±2,6 | 45,8±2,6 | 80,1±1,7 | 78,3±2,3 | 9,1±0,6 | 7,8±2,3 |
| II group (n=51) | 31,4±1,8 | 32,1±2,1 | 46,4±2,4 | 43,3±2,2 | 80,9±1,3 | 83,9±1,3 | 9,1±0,6 | 9,9±0,5 |

Note. *P<0,05

**Table 4**

**Blood nitric oxide content in the patients of both clinical groups**

| Therapy \ Group of patients | NO, mcmol/L | |
|---|---|---|
| | I group (n=32) | II group (n=33) |
| Prior to the therapy | 19,6±0,7 | 20,1±1,5 |
| Following the therapy | 25,9±2,9 | 18,6±0,4 |
| P | P<0,05 | P>0,05 |

Nucleinat, could be explained by a plausible reduction in the manifestations of chronic hypoxia, which is inherent to this disease [6].

Therefore, the use of Nucleinat in combined therapy for bronchial asthma ensures a significant reduction of the inflammatory process in children, manifested by lowered bronchial hyperresponsiveness, lowered oxygen-dependent bactericidal activity of neutrophils and reduced signs of chronic hypoxia (an elevated blood content of nitric oxide).

## Conclusions

1. The use of Nucleinat in combined therapy for bronchial asthma in children ensures a significant reduction in bronchial hyperresponsiveness. The risk of a reduction of bronchial hypersensitivity in the first clinical group of patients was higher relative to the children, receiving placebo (OR = 3,6; 95% CI: 1,3-9,3).

2. Following the use of Nucleinat, a clear trend was noted towards an elevated bronchodilation after $beta_2$-agonist inhalation.

3. The use of Nucleinat in combined therapy for bronchial asthma was accompanied with significant reductions in the parameters of oxygen-dependent bactericidal action of blood neutrophilic granulocytes. The probability of a decrease of the phagocytic activity in the Ist clinical group patients relative to the children receiving placebo, was increased (OR=1,9 with 95% CI (0,9-4,4)).

4. Following the use of Nucleinat, a clear trend was noted towards an elevated level of the blood nitric oxide.

**Perspectives of future investigations in this direction** are to estimate the effect of Nucleinat in the complex of control therapy of children's BA on the rate of the clinical signs.

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## КАКАЯ РОЛЬ НУКЛЕИНАТА В КОМПЛЕКСЕ КОНТРОЛИРУЮЩЕЙ ТЕРАПИИ БРОНХИАЛЬНОЙ АСТМЫ У ШКОЛЬНИКОВ? ДВАЖДЫ СЛЕПОЕ ПЛАЦЕБО–КОНТРОЛИРОВАННОЕ ИССЛЕДОВАНИЕ

***Л.О.Безруков, О.К.Колоскова, У.И.Марусик***

**Резюме.** Дважды слепым плацебо– контролированным методом проведено исследование влияния Нуклеината на гипервосприимчивость дыхательных путей, показатели фагоцитарной активности и фагоцитарного числа нейтрофилов, их кислородозависимого метаболизма и концентрации метаболитов оксида азота в крови в комплексном лечении бронхиальной астмы у 98 школьников. С помощью таблицы случайных чисел было сформировано две клинические группы. В первую клиническую группу вошли 47 больных, которые в комплексе базисной терапии принимали Нуклеинат в дозе 0,25 г в сутки в течение 21 дня. Вторую группу сформировали 51 школьник, которые получали плацебо. Показано, что благодаря использованию Нуклеината достигнуто снижение гипервосприимчивости дыхательных путей, а также оптимизации контроля этого заболевания, на что косвенно указывал прирост риска выявления умеренной восприимчивости бронхов к гистамину (СШ=3,6; 95 % ДИ: 1,3-9,3) и снижение фагоцитарной активности нейтрофилов (СШ=1,9 з 95 % ДИ (0,9-4,4)).

**Ключевые слова:** дети, бронхиальная астма, гипервосприимчивость бронхов, иммунитет, Нуклеинат.

## ЯКА РОЛЬ НУКЛЕЇНАТУ В КОМПЛЕКСІ КОНТРОЛЬОВАНОЇ ТЕРАПІЇ БРОНХІАЛЬНОЇ АСТМИ У ШКОЛЯРІВ? ДВІЧІ СЛІПИЙ ПЛАЦЕБО-КОНТРОЛЬОВАНИЙ МЕТОД

***Л.О.Безруков, О.К.Колоскова, У.І.Марусик***

**Резюме.** Двічі сліпим плацебо – контрольованим методом досліджено вплив Нуклеїнату на гіперсприйнятливість дихальних шляхів, показники фагоцитарної активності та фагоцитарного числа нейтрофілів, їх кисневалежного метаболізму та концентрації метаболітів монооксиду нітрогену в крові в комплексному лікуванні бронхіальної астми в 98 школярів. За допомогою таблиці випадкових чисел сформовані дві клінічні групи. До першої групи увійшли 47 осіб, які в комплексі базисної терапії приймали Нуклеїнат у дозі 0,25 г на добу протягом 21 дня. Другу групу сформували з 51 дитини, що отримували плацебо за тією ж схемою. Показано, що завдяки використанню Нуклеїнату досягнуте зниження гіперсприйнятливості дихальних шляхів, та оптимізацію контролю захворювання, на що опосередковано вказувало зростання ризику виявлення помірної сприйнятливості бронхів до гістаміну (СШ=3,6; 95 % ДІ: 1,3-9,3) та зниження фагоцитарної активності нейтрофілів (СШ=1,9 з 95 % ДІ (0,9-4,4)).

**Ключові слова:** діти, бронхіальна астма, гіперсприйнятливість бронхів, імунітет, Нуклеїнат.

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