# THE EFFECTS OF THE INHALATORY CORTICO THERAPY ON THE SOMATOTROPE AXES IN ASTHMATIC CHILDREN GROUPE OF AGE (0-18 YEARS) UNDER TREATMENT WITH INHALATORY CORTICOTHERAPY, PROSPECTIVE STUDY WITH CONTROL LOT

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*Abstract: This prospective study, assessing the growth of 106 asthmatic children age group 0-18 years old, in treatment with low and medium doses of different types of inhaled corticosteroids with different treatment durations, compared with a control group of 107 children without asthma and/or corticosteroids treatment, showed no statistically significant differences between average height, weight scores, in the study group but a statistically significant decrease in pulsatile secretion of growth hormone (GH), and a significant increase in serum alkaline phosphatase values, compared with control group ($p < 0.05$).*

*Rezumat: Studiul prospectiv de evaluare a creşterii unui lot de 106 copii astmatici cu vârste cuprinse între 0-18ani aflaţi în tratament cu corticosteroizi inhalatori diferiţi în doze mici şi medii, cu durate de tratament diferite, comparativ cu un grup de control 107 copii fără astm bronşic şi/sau corticoterapie arată că deşi nu există diferenţe semnificative statistic între mediile taliei, scorurile greutăţii, în lotul studiu există o scădere semnificativă statistic a secreţiei pulsatile a hormonului de creştere (GH), şi o creştere semnificativă a valorilor fosfatazelor alcaline serice, comparativ cu lotul martor ($p<0,05$).*

## INTRODUCTION

Corticosteroids have an important role in reducing inflammation in days or weeks and improving lung function in patients with asthma, and decreasing bronchial reactivity in a few months. They also significantly inhibit each component of the GH axis hormones: reducing GH's pulsatile release, lowering the expression of growth hormones, lowering IGF-1 bioactivity, inhibiting the activity of osteoblasts, suppressing collagen synthesis, adrenal androgen production, intestinal absorption of calcium, and promoting bone resorption and increasing urinary calcium excretion (1,2, 3,4,6,7)

In asthmatic children receiving inhaled corticosteroid treatment, an important problem is represented by the potential effects of inhaled corticosteroids on linear growth. (1,2,3,25)

## PURPOSE OF THE STUDY

The data mentioned in various randomized control group studies, published in various medical databases and prestigious journals in the world for almost 30 years and so far(25) show linear growth impairment at high doses of inhaled corticosteroids and a minimum effect on linear growth using both small and medium doses (1,3,6,7,9,10,12,15,19,20,23). Reductions were observed of aproximately 1 cm in the first year of treatment in children but the final height was reached (1). According to the recommandations of Expert Panel Report 3 2007 (1, 25) growth in asthmatic children with inhaled corticotherapy must be monitored , and should be monitored by knemometry , with stadiometers and as much as possible by the same person in each visit.

The study was conducted on asthmatic patients being in treatment with inhaled corticosteroids in various doses (small and medium) and at different durations of treatment when the samples were harvested, using as control group patients with various intercurrent respiratory problems but without asthma and/or corticosteroids orally, inhaled, or parenterally. The major objective was to evaluate growth in both groups by measuring anthropometric parameters (height-T, weight-G, body mass index-BMI) and the biological parameters such as growth hormone GH dosage (two determinations), IGF-1 secretion (1determination ) and serum levels of phosphatase alacaline - FAS.

## MATHERIAL AND METHOD

The prospective study was conducted on a group of 213 patients. The study group, 106 asthmatics aged between 0-18 years, was divided in three major age groups 0-5 years, 5-13 years, 13.6-19 years, a sex ratio M:F of approximately 1:1, and at the moment of colecting the blood samples they were treated at low and medium doses of inhaled corticosteroids , with different durations of treatment up to that time (less than 3 months, 3-6 months, 6-12 months, more than 12 months). The control group - 107 patients without asthma without corticosteroids, were also divided into three major age groups 0-5 years, 5-13 years, 13.6 years-19 years, with a sex ratio M:F of approximately 1 1.

**The criteria for inclusion** : both the study group and the control group entered the study only if there were normal levels for T3, T4, TSH, SGOT, SGPT, PT, glucose, ureea(bun), creatinine, Ca, Mg, normal urine exams, normal-sized parents, proper nutrition status, normal diet for each patient (3,12, 18)

**Study exclusion criteria** were represented by abnormal levels (increased or decreased values of the parameters mentioned above ), a medical history of low birth weight or smaller family heights, metabolic diseases, genetic diseases, chronic inflammatory diseases, positive heterophile antibody (18)

**Method** In both groups, for each case were measured the followings: GH (two successive determinations at a 120.min

interval, the first measurement in 09.00 am, in a state of rest), IGF-1 (a single determination), T3, T4, TSH, SGOT, SGPT, PT, glucose, ureea, creatinine, Ca, Mg, FAS, urine exams . Blood samples were also collected for performing blood counts. The heights (T) were measured with the same stadiometer and that same infant stadiometer and for weight (G) using the same scale. For hormonal dosage (GH, IGF-1, T3, T4, TSH) an chemiluminescence immunoassay was used for detection .

     **The statistical methods** used (27,28) were based on studies of the distribution in the first phase for each parameter (both anthropometric variables and biological ones) in order to establish if there is a normal distribution, uniform, poisson or exponential) with the Kolmogorov-Smirnov testing for a sample. If the value of this test "asymp. Sig (2-tailed)" was less than 0.05 (p <0.05) it was statistically significant and the test had 95% of confidence . For this situation we have rejected the null hypothesis (normal distribution) and we have accepted the alternative hypothesis (different from the normal distribution). For variables with normal distribution, T test was applied to test whether the media of the two groups were equal and the test is statistically significant if there is a statistically significant difference between the averages of two groups(p <0.05). For variables with uneven distribution with the test Mann-Whitney U we have verified if the study group ranks are much higher ranks or lower than the ranks of the control group, without testing the differences between the means of the test (the test is statistically significant if p <0.05). It was considered useful to assess in both the study and the control group the GH1, GH2 respectively with normal or low values (<1ng/ml or > 1/ng/ml), IGF-1 (low range or below the median), FAS (normal or elevated) using a binomial test for which the null hypothesis that refers to the two categories have equal chances of occurence for each group . A p value < 0.05 express the tendancy of occurring in a particular group

## RESULTS

1. In the category of GH1 less than 1 ng/ml, the number of patients in the study group did not differ statistically significant with the number of patients in the control group (p> 0.05). Regarding the category of GH1 more than 1ng/ml in the study group also, there was no statistically significant difference with the number of patients in the control group (p> 0.05)
2. In the category of GH2 less than 1 ng/ml, the number of patients in the study group was statistically bigger than the

number of patients in the control group (p< 0.05). Regarding the category of GH2 more than 1ng/ml in the study group there was also a statistically significant difference ( a lower number ) than the number of patients in the control group (p< 0.05) see table 1

3. In the category of low IGF-1, the number of patients in the study group was significantly lower than the number of patients in the control group (p <0.05) and in the category of IGF-1 in range but below the median, the number of patients in the study group did not differ significantly from the number of patients in the control group (p> 0.05)
4. In the category with normal ALP , the number of patients in the study group is significantly lower than the number of patients in the control group (p <0.05) and in the category with ALP increased, the number of patients in the study group was significantly higher than the number patients in the control group (p <0.05)
5. The variable height had a normal distribution (p> 0.05). T test for independent samples revealed that the average height of the control group was not significantly different from the average height of the study group (p> 0.05) (see Table 3)
6. The variable weight had a normal distribution. Mann-Whitney U test for independent samples revealed that scores for weight in the control group scores were not significantly different than the scores for weight in the study group (p> 0.05)

## DISCUSSIONS AND CONCLUSIONS

1. Small and medium-dose corticosteroids having minimal effects as many authors concluded (1) still have the potential to reduce even at low or medium doses, in the asthmatic patients compared to the control group, the pulsed secretion of growth hormone but regarding anthropometric measurements there is no statistically significant difference between the height averages in study group compared to the control group or for the scores of weights in the control group compared to the study group .
2. It is difficult to assess if the IGF-1 secretion is impared because the number of patients with IGF-1 below the median but in normal range) in study group, did not differ significantly from the control group and the numbers with low levels of IGF-1 for both groups were not statistically significant

**Table no. 1. Categories GH1,GH2: (< 1 means low levels, >1 normal levels ), Asy sig- p represents statistical significance, SG-study group, CG-control group )**

| Parameters | GH1<1 | | | GH1>1 | | | GH2<1 | | | GH2 >1 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | LS | LM | Asy sig-p | LS | LM | Asy sig-p | LS | LM | Asy sig-p | LS | LM | Asy sig-p |
| No .pacients / p | 68 | 57 | ,371 | 38 | 49 | ,284 | 74 | 27 | ,000 | 31 | 75 | ,000 |

**Table no. 2. Categories : IGF-1 low or in range but below the median value , ALP – normal or elevated**

| Parameters | IGF-1 low | | | IGF-1 in range below the median | | | ALP normal | | | ALP increased | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | LS | LM | p | LS | LM | p | LS | LM | p | LS | LM | P |
| Nr .pacienţi/ p | 4 | 14 | ,031 | 35 | 44 | ,368 | 37 | 91 | ,000 | 69 | 19 | ,000 |

**Table no. 3. Test T (Height )**

| Parameter | Group | Number of patients | Media | Standard deviation | t | p value |
|---|---|---|---|---|---|---|
| Height | Study | 106 | 130,12 | 21,24 | **1,430** | **,154** |
| Height | Control | 107 | 125,95 | 21,33 | | |

**Table no. 4. Mann- Whitney U test for independent samples**

| Parameter | Lot | N | Mean Rank | Sum of ranks | Mann-Whitney U | Z | P value |
|---|---|---|---|---|---|---|---|
| Weight | Study | 106 | 106,31 | 11268,50 | 5597,500 | **-,163** | **, 870** |
| Weight | Control | 107 | 107,38 | 11522,50 | | | |

In conditions which may rule out other causes of growth of alkaline phosphatase values and normal values for calcium and magnesium, serum alkaline phosphatases may be considered useful markers for monitoring the speed of growth and the effects of corticosteroid on growth and bone metabolism. (15,16,17,18,21,22,23,24)

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