DOCTORATE THESIS

THE INFLUENCE OF INHALED CORTICOSTEROIDS ON GROWTH AND DEVELOPMENT RATES IN ASTHMATIC CHILDREN

ABSTRACT

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TABLE OF CONTENTS

The present paper comprises 286 pages. It is structured in two parts:

A. The general part;
B. The special part.

In the general part there are presented general considerations regarding the infantile asthma from the perspective of the latest research in the field, and also a statistical synthesis. In the special part there are presented, in detail, the objectives, methodology, results and general conclusions and recommendations regarding the management of the asthmatic children under treatment with inhaler corticosteroids.

The scientific justification of the paper. Asthma is a global public health problem, affecting all ages and social categories. It is estimated that, worldwide, there are approximately 300 million people suffering from asthma, and their number is doubling every 10 years. Asthma causes a significant social and economic impact that has led to the establishment of intercontinental and inter-state coalitions to manage this disease.

In the last two decades, many studies have tried to evaluate the efficiency and safety of the inhaler corticosteroid therapy. The majority of the clinical trials assessing the growth rate in children were performed by measuring one or two anthropometric indices. Studies by Zhang and Teper (2011), Teper (2011), Barnes and Hocks (2008), Hansell and Thumerell (2004) and other researchers indicate that the therapy with low-dose corticosteroids administered as first-line is the preferred for a long time treatment, this one being less influential on the children growth rate.

Other researchers like Brandt and Martinez (2011), Creese (2001) and Miller (2000) identify a decrease of the growth process for the asthmatic children, an effect which depends on the daily dose and they recommend a cut of the doses and precaution in their long-term administration. Under the circustances in which the results of the studies are inconsistent, many doctors keep themselves reserved in what regards the long-term inhaler corticosteroid therapy. The acknowledgement of the possible consequences of the therapy over the growth and development of the children is an essential factor to be taken in consideration by the public health politics in the conditions in which, the bronchial asthma represents the most important chronical pathology of a child.

The originality of this paper is given by the attempt to realize a complex image over the impact of the corticosteroid therapy throughout the evaluation of an increasing number of antropometric factors. The results of the study have an immediate applicability and they represent a scientific base for the selection of the long-term therapy bronchial infantile asthma. In the same time, the study offers a practical supervision model which can be used for the evaluation of the possible adverse reactions of other therapies.

The general objective of this paper is to identify the effect of the inhaler corticotherapy on a long-term over the somatic growth and development of children suffering of soft and moderate bronchial asthma.

Secondary objectives: 1. The evaluation of the effect of the corticotherapy over the growth rate of the longitudinal dimensions of the body; 2. The evaluation of the effect of the corticotherapy over the growth rate of the circular dimensions (circumferences, perimeters) of the body; 3. The specification of some recommendations regarding the management of the somatic growth of the asthmatic children under corticosteriod therapy.

The material and work methodes: the research has been made having as a ground basis the design of a clinical, observational, analitical and prospective study, carried out at the Clinical Pediatric Hospital in Sibiu and at its Pneumology ambulatory. The study period was

2004-2011. The study has been carried out respecting the ethic research principles on human subjects.

The study material has been divided into two batches: ***Batch A***, n=100 subjects, diagnosed with bronchical asthma, under continuous therapy with inhaler corticoids.

Criteria of selection: age between 5-19 years; persistent bronchial asthma in a soft or moderate form under continuous therapy of at least 2 years with inhaler corticods administred in small doses with a frequency of 1-2/ day.

Exclusion criteria: the co-existence of cronical diseases which affect the growing process; the presence of the ax deviation at the level of different body segments; vicious positions (body breaks, muscular retractions, vicious consolidate fractures); the subjects suffering from bronchial asthma with a soft or moderate form, under treatment with inhaler corticosteroids administred in small doses, but which hadn't a continuity of two years or which did not respect the indicated posology; general corticotherapy: current or past medication which might have as an adverse effect the infuence over the somatic growth and development.

Batch B (witnesses), n=100 healty subjects.

Criteria of selection: age between 5-19 years; subjects which do not suffer of any cronical deseases or constitutional pathology that affect the growing process.

Exclusion criteria: subjects which, during the research process, were taken into evidence with cronical diseases or constitutional pathology that affects the growing process (n=0); the presence of the ax deviation at the level of different body segments; vicious positions; current or past medication which might have as an adverse effect the infuence over the somatic growth and development.

The sample basis for the two batches were represented by: children aged 5-19 years suffering of bronhical asthma and identified on the basis of the medical papers of the Clinical Pediatric Hospital in Sibiu and from its specialty ambulatory, from the family doctor practices from batch A; children aged 5-19 years under the evidence of the local pre-universitary education institutions for batch B. The distribution of the subjects in the two batches was made at random. Both batches were subdivized in five age groups: a. 5 and 8 years; b. 8 years and 1 day - 10 years; c. 10 years and 1 day - 13 years; d. 13 years and 1 day - 16 years; e. 16 years and 1 day - 19 years. The batches are homogenous from the point of view of the subject distribution on age and sex ratio.

The parameters studied were represented by the main antropometric features for the evaluation of the somatic growth and development: 1. Longitudinal dimensions of the linear growth evidence – total height (waist); the length of the shank; the length of the plant; 2. circular dimensions for the evidence of the circumference growth – the torax circumference; the hip circumference; the arm circumference; the shank circumference; the skull circumference. The measurements were made periodically, once in 6 months, respecting the same hour intervals. The devices used: the antropometer, the flexible centimeter and the micrometer. For the precision and safety of the measurement, the tests were made by two independent operators using the same devices.

The final data were registered on a table work paper containing the infobiographical and antropometrical data of the subject and they were expressed through graphic shapes. The statistic analysis was carried out using the statistic package SPSS, variation 10, the centrality/ deviation indicator used was the arithmetical average and the standard deviation; we have calculated the growth differences, the average of the growth differences and **p** in the case of each age group; in the same time, in order to point out the homogenity of the batches, we used the correlation coeficient.

The level results of the research were dispensed through the publication of scientific articles and the communication through some scientific manifestations.

Results and discussions

The evaluation of the height growth (p>0,92 for all age groups) **and of the rate of the shank length growth** (p>0,86 for all age groups) have indicated that there are no significant differences from a static point of view between the two batches.

Table no.1. The averages of the growth differences of the waist on age groups

Age group		5 – 8 years		8 years and a day – 10 years		10 years and a day – 13 years		13 years and a day – 16 years		16 years and a day – 19 years	
Batch		S	M	S	M	S	M	S	M	S	M
The average of growth difference	1 year	2.33	2.43	1.18	1.24	0.65	0.65	1.14	1.14	0.44	0.44
	2 years	4.6	4.68	2.17	2.25	1.03	1.1	2.38	2.41	0.83	0.87
p -> t-test		0.96		0.93		0.92		0.99		0.95	

Table no. 2. The average of the growth differences of the shank on group ages

Age group		5 – 8 years		8 years and a day – 10 years		10 years and a day – 13 years		13 years and a day – 16 years		16 years and a day – 19 years	
Batch		S	M	S	M	S	M	S	M	S	M
The average of growth difference	1 year	0.45	0.47	0.41	0.43	0.4	0.41	0.48	0.52	0.36	0.4
	2 years	0.83	0.83	0.76	0.79	0.72	0.73	0.83	0.84	0.67	0.72
p -> t-test		0.97		0.93		0.97		0.93		0.86	

The evaluation of the plant length growth identifies a minimum variation of the average of the growth differences for the age group 10 years and one day – 13 years, where p=1 and the lack of the differences statistically significant for the rest of the age groups (p>0,85).

Table no .3. The average of the gowth differences of the plant on age groups

Age group		5 – 8 years		8 years and a day – 10 years		10 years and a day – 13 years		13 years and a day – 16 years		16 years and a day – 19 years	
Batch		**S**	**M**	**S**	**M**	**S**	**M**	**S**	**M**	**S**	**M**
The average of growth difference	**1 year**	**0.3**	**0.32**	**0.29**	**0.3**	**0.29**	**0.28**	**0.31**	**0.33**	**0.26**	**0.3**
	2 years	**0.59**	**0.63**	**0.57**	**0.59**	**0.55**	**0.56**	**0.6**	**0.64**	**0.49**	**0.52**
p -> t-test		**0.90**		**0.95**		**1.00**		**0.90**		**0.85**	

The evaluation of the thorax circumference growth (p>0,91 for all age groups), **hip** (p>0,84 for all age groups**), arm** (p>0,85 for all age groups**), shank** (p>0,86 for all age groups**)** and **the skull** (p>0,91 for all age groups**)** do not register differences statistically different for the two batches.

Table no.4. The average of the gowth differences of the thorax on age groups

Age group		5 – 8 years		8 years and one day – 10 years		10 years and one day – 13 years		13 years and one day – 16 years		16 years and one day – 19 years	
Batch		S	M	S	M	S	M	S	M	S	M
The average of growth difference	1 year	0.44	0.47	0.42	0.43	0.37	0.4	0.43	0.44	0.35	0.37
	2 years	0.83	0.87	0.8	0.81	0.76	0.78	0.81	0.83	0.78	0.79
p ->t - test		0.91		0.97		0.94		0.96		0.96	

Table no.5. The average of the gowth differences of the hip on age groups

Age group		5 – 8 years		8 years and one day – 10 years		10 years and one day – 13 years		13 years and one day – 16 years		16 years and one day – 19 years	
Batch		S	M	S	M	S	M	S	M	S	M
The average of growth difference	1 year	0.7	0.6	0.56	0.57	0.4	0.44	0.65	0.69	0.34	0.37
	2 years	1.24	1.19	1	1.01	0.7	0.76	1.07	1.12	0.62	0.66
p ->t - test		0.87		0.98		0.84		0.89		0.96	

Table no. 6. The average of the gowth differences of the arm on age groups

Age group		5 – 8 years		8 years and one day – 10 years		10 years and one day – 13 years		13 years and one day – 16 years		16 years and one day – 19 years	
Batch		S	M	S	M	S	M	S	M	S	M
The average of growth difference	1 year	0.4	0.42	0.39	0.4	0.38	0.39	0.4	0.42	0.32	0.36
	2 years	0.77	0.8	0.74	0.78	0.67	0.71	0.72	0.75	0.63	0.69
p -> t-test		0.93		0.93		0.92		0.92		0.85	

Table no.7. The average of the gowth differences of the shank on age groups

Age group		5 – 8 years		8 years and one day – 10 years		10 years and one day – 13 years		13 years and one day – 16 years		16 years and one day – 19 years	
Batch		S	M	S	M	S	M	S	M	S	M
The average of growth difference	1 year	0.37	0.39	0.33	0.35	0.31	0.32	0.36	0.37	0.27	0.3
	2 years	0.7	0.72	0.62	0.65	0.6	0.61	0.64	0.68	0.55	0.6
p -> t-test		0.94		0.92		0.97		0.92		0.86	

Table no. 8. The average of the gowth differences of the shank on age groups

Age group		5 – 8 years		8 years and one day – 10 years		10 years and one day – 13 years		13 years and one day – 16 years		16 years and one day – 19 years	
Batch		S	M	S	M	S	M	S	M	S	M
The average of growth difference	1 year	0.34	0.35	0.3	0.31	0.29	0.3	0.32	0.33	0.27	0.29
	2 years	0.71	0.73	0.61	0.64	0.56	0.6	0.68	0.7	0.55	0.57
p -> t test		0.96		0.94		0.91		0.96		0.93	

General conclusions:

1. The study of the linear growth parameters allows the appreciation of the effects of the CSI therapy over the growth rate. Regarding the waist, out of the resulted values, we have noticed a slight influnce of the growth rate for the subjects treated with CSI, in comparison with those belonging to the witness batch, the growth difference being of maximum 1 mm, after one, respectively two years, $p > 0.85$.
2. The influence of the growth rate of the waist for the subjects treated with CSI is not significat from a statistic point of view.
3. The average of the length of the shank for the subjects treated with CSI, in comparison with those of the witness batch was smaller with maximum 0.5 mm after one, respectively two years of treatment, with $p > 0.86$.
4. The influence of the growth of the shank of the subjects treated with CSI is not significant from a statistic point of view.
5. In the case of the plant, the growth was smaller in the case of the children treated with CSI, in comparison with the witness batch, with values of maximum 0.4 mm after one year, and 0.6 mm after two years of treatment, with $p > 0.85$.
6. The inhaler corticosteroids don't affect the length growth of the plant.
7. In the case of the circumference of the thorax, the average of the growth difference was smaller for the subjects treated with CSI in camparison with those from the witness batch with values of maximum 0.3 mm after one year, and 0,4 mm after two years of treatment with $p > 0.91$.
8. The inhaler corticosteroids don't affect the length growth of the thorax circumference.
9. In the case of the circumference of the hip, the average of the growth difference was smaller for the subjects treated with CSI in camparison with those from the witness batch with values of maximum 1 mm after one year, and 0,6 mm after two years of treatment with $p > 0.84$.
10. The inhaler corticosteroids determine a insignificant reduction of the hip circumference.

11. Regarding the arm circumference, we have noticed a slight affection of the growth process for the subjects treated with CSI, in comparison with those in the withness batch, a decrease of maximum 0,2 mm after one year, and 0,6 mm after two years of treatment with $p > 0.85$.
12. The inhaler corticosteroids don't affect the growth of the arm circumference.
13. In the case of the shank circumference, the average of the growth difference was bigger for the subjects of the witness batch in comparison with those under inhaler corticotherapy, with values of maximum 0,3 mm after one year, and 0,5 mm after two years of treatment with $p > 0.86$.
14. The inhaler corticosteroids don't affect the growth of the shank circumference.
15. In the case of the skull circumference, the average of the growth difference was smaller for the children treated with CSI, in comparison with those in the witness batch, with values of maximum 0,1 mm after one year, and 0,4 after two years of treatment with $p > 0.91$.
16. The inhaler corticosteroids don't affect the growth of the skull circumference.
17. The growth process of the children treated with inhaler corticosteroids in small doses, during two years, is not significantly influenced.
18. The growth rate for the studied subjects was similar with the literature data which indicate a stressed growth and development during the ages of 10-15.
19. The results of the study allow us to sustain under no doubt the use, for the asthmatic pacients, of inhaler corticosteroids in small doses, during a long period of time.

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