Long term inhaled corticosteroids in childhood asthma:

Impact on growth and adrenocorticol function

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Abstract

Inhaled corticosteroids have a marked effect on both the immediate and the long-term aims of asthma therapy. This study aims to assess safety and efficacy of inhaled corticosteroids in childhood asthma through studying the effect of its long term use on growth and serum cortisol level. This study included 60 children (40 boys and 23 girls), aged 3 -10 years , did not receive systemic corticosteroids and not suffering from any other systemic chronic diseases.The children were classified into group1 (30 asthmatic patients on ICS) and group 2 (33 asthmatic patients not received ICS). All children were subjected to full clinical examination, radiological studies, anthropometric measurements (weight, height, sitting height, ; triceps and subscapular skin fold thickness, mid upper arm, waist, hip, and chest circumferences) and laboratory investigation includes serum cortisol. Then, the body mass index was calculated. The results showed that there is no significant difference in anthropometric measurements and serum cortisol level between the two groups; these results support the safety of ICS on growth. Moreover, we found that the height of group 2 (children not on ICS) are shorter than group 1 (patient on ICS). In conclusion: Inhaled glucocorticosteroids are the most effective controller therapy, and are therefore the recommended treatment for asthma for children. [Report and Opinion. 2010;2(3):23-35]. (ISSN: 1553-9873).

Key Words: Asthmatic children- anthropometric measurement- cortisol level.

INTRODUCTION

Inhaled corticosteroids (ICS), which reduce both the morbidity and the mortality that are associated with asthma (Suissa etal.,2000), are recommended as first-line therapy for persistent asthma of all severities (NAEP, 2002 and GINA 2006). Consequently, ICS have become more widely used, often commencing in children aged <5 years, and for long, seamless periods (Stafford etal., 2003). However, a potential safety concern of ICS use for systemic adverse events in children is

growth and adrenal gland suppression, which may limit appropriate ICS use by physicians and individuals and, thus, the attainable therapeutic benefits. Such effects, however, are potentially transient, affording no effect on finally attained adult height (Agertoft and Pedersen,2000).

In 1998, the Food and Drug Administration (FDA) reviewed all inhaled and intranasal corticosteroid growth studies in pediatric patients. All marketed ICS showed evidence of a small effect on growth in studies with major design flaws (Kennis,1998). As a result, precautionary labeling regarding growth suppression was implemented for the entire class, and draft guidance for the conduct of future growth studies was issued (FDA,2007).

Adrenocortical function in form of serum cortisol level is another important point to discuss in children treated with ICS. Some investigators have found mild to moderate suppression of adrenal function while others have normal adrenal function (Allen, 2006).

The purpose of this research is to assess safety and efficacy of inhaled corticosteroids in childhood asthma through studying the effect of its long term use on growth and serum cortisol level.

Materials and Methods

Patients:

This data was obtained from a case control survey of a sample of 63 Egyptian children (40 boys and 23 girls) aged 3-10 years (mean age 6.65 yrs). They are recruited from the allergy clinic at the New Children's Hospital, Cairo University. Patients were required to demonstrate effective use of metered- dose inhaler (MDI) devices for inclusion; patients unable to or who refused to use study devices as required were excluded from the study. Patients who were using noncorticosteroid asthma medication on an as-needed or daily basis or low ICS dosage were included. Informed consent was obtained from patients' parents or legal guardians. All protocol and informed consent forms were approved by National Research Center Ethitical Commity.

Patients were classified into two groups:

1 : Group 30 child on inhaled corticosteroids for at least one year.

Group 2 : 33 child not on ICS.

The children were classified according to their sex into two groups, males and females. Then they re-classified into two groups according to the dose of ICS (=100 µg and > 100 µg budesonide and beclomethason propionate). Their asthma were also classified according to severity classification of asthma into mild, moderate and severe following the severity classification of Global Initiative for Asthma (GINA 2006).They did not receive systemic corticosteroids and not suffering from other systemic chronic diseases.

Study design:

The following were performed for each child:

-A sample questionnaire was directed to the parents about the medical history of the child with special emphasis on any chronic disease or long-term systemic treatment.

-Complete clinical examination to exclude other chronic systemic diseases that may affect growth.

-Radiological studies: plain X-ray both posterior-anterior and lateral views were

done to exclude any other chest or heart disease.

-Anthropometric assessment (growth data): was then attemped using standardized equipment, following the recommendations of the International Biological Program (Hiernau and Tanner, 1969). Three consecutive measurements were taken and when the difference between the readings was acceptable the mean was recorded. Body weight was measured with minimal clothing (for which no correction was made) using Seca scales and approximated to the nearest 0.01Kg..Height and sitting height were measured without shoes using a Holtain portable anthropometer and approximated to the nearest 0.1 cm. The mid upper arm, waist, hip, and chest circumferences, were taken using a flexible nonstretchable plastic tape and approximated to the nearest 0.1cm. Triceps skin fold, Subscapular and suprailiac skinfold thickness were measured on the left side of the body using Harpenden skinfold caliper and approximated to the nearest 0.2 mm. Then The body mass index was calculated [Weight (Kg) / Height ^{2} (m)] .

-Laboratory investigation: morning blood sample (3ml) was withdrawn from each child into a plane tube, after clotting; the serum were separated by centrifugation and was stored at -20 C until assayed for determination of serum cortisol accomplished by using the UBI MAGIWEL CORTISOL Quantitative test, which based on the principle of competitive solid enzyme immunoassay.

Statistical analysis:

The z score (SDS) of the anthropometric measurements of the asthmatic children were calculated to eliminate the effect of age and sex for all groups. Mean and standard deviation for all studies parameters were calculated for each age and sex separetly. Students t test was used to asses the statistical significance of difference in the z score of the anthropometric measurements and serum cortisol level between the two groups and between males and females in the study sample. One way ANOVA (analysis of variance) was done to test the significance of the z scores in the different levels of sevirety of asthma. Correlation between duration and doses of treatment with ICS and the z score of anthropometric measurements and serum cortisol level was done uses coefficient of variation. The statistical package of social science "SPSSIPC" software version 9.05 program was used.

Results

Comparison of anthropometric measurements and serum cortisol level between the two sex groups of all study sample amonge Egyptian asthmatic children recorded nosignificant effect (table1).While on comparing the anthropometric measurements and serum cortisol between the two groups of the study (table 2) showed only a significant difference in height of group 1(on ICS) (p=0.013).

Regarding the dose of inhaled corticosteroids (table 3) there were a significant difference in hip circumference (p=0.03) and chest circumference (p=0.002) in those patients using a dose more than 100 µg. However, those using ICS for more than 12 months showed a significant difference in waist circumference (p= 0.02)(table 4).

It was observed that there is no significant difference in the anthropometric measurements and serum cortisol level regarding the degree of severity of asthma (table5). The correlation between

anthropometric measurements, serum cortisol level, treatment duration, the dose of ICS and age (table 6) showed that there was a significant negative correlation between treatment duration and only with sub scapular skin fold; and between age, weight, sitting height, triceps and sub scapular skin fold thickness. There was a significant positive correlation between dose the dose of ICS with chest, hip and waist circumferences.

Table (1): Comparison of anthropometric measurements and serum cortisol level between the two SEX groups of all study sample among Egyptian asthmatic children

	Male(n=40)		Female (n=23)		Pvalue
	Mean	SD	Mean	SD	
AGE	7.03	2.16	5.99	2.11	0.067
Weight	-0.09	0.93	0.08	0.95	0.47
Height	-0.32	1.43	-0.20	1.23	0.72
Sitting height	-0.09	1.32	-0.03	1.15	0.85
Body mass index	-0.04	1.16	0.25	1.10	0.33
Triceps skin fold	0.49	1.21	0.57	0.92	0.77
Sub scapular skin fold	0.34	1.11	0.58	1.03	0.39
Mid upper arm circumference	-0.56	0.95	-0.52	0.95	0.87
Waist circumference	-0.21	1.18	-0.23	0.81	0.95
Hip circumference	-0.08	1.00	-0.15	0.86	0.77
Chest circumference	-0.82	1.33	-0.05	1.06	0.14
Serum cortisol	9.06	5.30	8.32	4.89	0.58

NB: ** (Significant if $p \leq 0.05$)

Table (2): Comparison of anthropometric measurements and serum cortisol level between the two groups of the study sample among Egyptian asthmatic children

	Group on ICS (n=3o)		Group not on ICS (n=33)		P value
	Mean	SD	Mean	SD	
AGE	6.74	2.34	6.57	2.06	0.76
Weight	0.19	0.93	-0.23	0.90	0..069
Height	0.16	1.31	-0.67	1.29	0.013**
Sitting height	-0.02	1.23	-0.11	1.29	0.78
Body mass index	0.15	1.33	0.00	0.95	0.59
Triceps skin fold	0.74	1.29	0.32	0.88	0.13
Subscabular skin fold	0.57	1.12	0.29	1.05	0.29
Mid upper arm circumference	-0.31	1.12	-0.75	0.70	0.062
Waist circumference	-0.20	0.89	-0.22	1.20	0.95
Hip circumference	-0.09	0.88	-0.12	1.01	0.93
Chest circumference	-0.37	1.40	-0.53	1.15	0.77
Serum Cortisol	7.75	4.02	9.73	5.86	0.12

NB: ** (Significant if $p \leq 0.05$)

Table (3): Comparison of anthropometric measurements and serum cortisol level in children on inhaled corticosteroids according to dose of ICS

	Dose= 100 µg (n=18)		Dose> 100 µg (n=12)		P value
	Mean	SD	Mean	SD	
AGE	6.56	2.27	7.02	2.52	0.61
Weight	0.10	1.05	0.33	0.74	0.48
Height	0.06	1.48	0.31	1.04	0.58
Sitting height	0.06	1.27	-0.13	1.21	0.68
Body mass index	0.06	1.55	0.29	0.96	0.62
Triceps skin fold	0.73	1.45	0.76	1.06	0.95
Sub scapular skin fold	0.55	1.17	0.60	1.08	0.91
Mid upper arm circumference	-0.18	1.20	-0.51	1.01	0.42
Waist circumference	-0.45	0.80	0.16	0.91	0.07
Hip circumference	-0.37	0.67	0.32	1.02	0.03**
Chest circumference	-1.00	1.00	1.32	0.61	0.00**
Serum cortisol	7.00	2.12	8.88	5.78	0.22

NB: ** (Significant if $p \leq 0.05$)

Table (4): Comparison of anthropometric measurements and serum cortisol level in children on inhaled cortiocosteroids according to duration of treatment with ICS

	Duration=12 months (n=17)		Duration >12 months (n=13)		P value
	Mean	Std. Deviation	Mean	Std. Deviation	
AGE	6.48	2.34	7.08	2.41	0.50
Weight	0.44	1.12	-0.13	0.44	0.07
Height	0.18	1.59	0.13	0.87	0.91
Sitting height	-0.24	1.39	0.27	0.95	0.25
Body mass index	0.40	1.63	-0.18	0.72	0.21
Triceps skin fold	1.11	1.44	0.27	0.90	0.06
Sub scapular skin folf	0.87	1.14	0.19	0.99	0.10
Mid upper arm circumference	0.08	1.25	-0.82	0.68	0.09
Waist circumference	-0.31	0.71	-0.07	1.09	0.02**
Hip circumference	-0.22	0.62	0.07	1.15	0.48
Chest circumference	-0.52	1.50	-0.18	1.41	0.39
Serum cortisol	7.48	2.80	8.10	5.33	0.68

NB: ** (Significant if $p \leq 0.05$)

Table (5): comparison of anthropometric measurements and serum cortisol level according to severity of asthma

	Mild (n=6)				Moderate(n=46)				Severe(n=11)				
	Mean	SD	Mini-Mum	Max-mum	Mean	SD	Mini-mum	Max-mum	Mean	SD	Mini-mum	Max-mum	Sig.
Age	6.92	2.25	4.00	10.00	6.70	2.21	3.00	10.00	6.32	2.21	4.00	10.00	0.84
Weight	-0.34	0.65	-1.25	0.44	0.05	0.96	-1.46	3.05	-0.17	0.96	-1.56	1.35	0.55
Height	-0.58	1.15	-1.76	1.26	-0.27	1.14	-2.64	1.89	-0.16	2.19	-3.16	3.42	0.83
Sitting Height	0.20	1.08	-1.06	1.57	-0.01	1.24	-2.84	2.10	-0.45	1.41	-2.52	1.68	0.51
Body mass index	-0.03	1.02	- 1.16	1.43	0.17	1.20	-2.13	4.78	-0.29	0.92	-1.76	1.47	0.48
Triceps Skin fold	-0.13	0.69	-0.83	0.78	0.56	1.16	-1.02	4.95	0.72	0.99	-1.05	2.06	0.29
Subscabular Skin fold	-0.16	0.65	-0.82	0.75	0.45	1.13	-0.86	3.20	0.62	1.02	-0.86	1.94	0.35
Mid upper arm circum-ference	-1.05	0.34	-1.46	-0.57	-0.50	0.99	-2.76	2.91	-0.42	0.95	-2.01	1.65	0.37
Waist Circumference	-0.29	0.78	-1.50	0.45	-0.26	1.00	-2.45	2.27	0.00	1.43	-1.82	3.77	0.76
Hip Circumference	-0.42	0.61	-1.35	0.26	-0.13	0.89	-1.93	2.15	0.15	1.29	-1.66	3.03	0.49
Chist Circumference	0.41	0.37	0.15	0.67	-0.68	1.29	-2.42	1.99	-0.06	1.23	-2.17	0.83	0.38
Serum Cortisol	11.17	7.79	4.00	25.40	8.98	5.21	4.00	27.60	6.68	1.46	5.00	9.20	0.20

Correlation is significant at the 0.05 level (1-tailed) ** Correlation is significant at the 0.01 level (1-tailed)

Table (6): correlation between anthropometric measurements and serum cortisol level, dose of ICS and duration of treatment

		Serum cortisol	Zwt	ZHt	ZSitHt	ZBMI	ZTSF	ZSSF	ZMU-AC	ZWC	ZHIPC	ZCC
Treatment duration	**Pearson Correlation**	-0.13	-0.11	0.08	0.05	-0.11	-0.24	-.320(*)	-0.13	0.12	0.20	0.33
	Sig. (1-tailed)	0.25	0.28	0.33	0.39	0.27	0.10	0.04	0.25	0.27	0.14	0.16
Dose	**Pearson Correlation**	0.10	0.09	0.16	-0.10	0.04	-0.05	-0.04	-0.12	.498(**)	.527(**)	.775(**)
	Sig. (1-tailed)	0.30	0.31	0.20	0.31	0.43	0.39	0.43	0.27	0.00	0.00	0.00
Serum cortisol	**Pearson Correlation**	1.00	-0.03	-0.03	0.04	0.02	-0.08	-0.02	-0.07	0.01	0.15	-0.25
	Sig. (1-tailed)		0.42	0.41	0.39	0.44	0.26	0.43	0.29	0.49	0.13	0.13
Age	**Pearson Correlation**	-0.02	-.227(*)	-0.04	-.327(**)	-0.18	-.351(**)	-.475(**)	0.01	0.07	0.08	0.01
	Sig. (1-tailed)	0.43	0.04	0.39	0.00		0.00	0.00	0.46	0.29	0.27	0.48

Correlation is significant at the 0.05 level (1-tailed) ** Correlation is significant at the 0.01 level (1-tailed)

Z score of Wt : weight, Ht: height, SitHt: sitting height, BMI: body mass index, TSF: Triceps Skin fold, SSF: Subscabular Skin fold , MUAC:Mid upper arm circumference, WC:Waist Circumference, HIPC: Hip Circumference,

CC: Chist Circumference

DISCUSION

Asthma is a worldwide problem with an estimated 300 million affected individuals. Nonetheless, based on the application of standardized methods to measure the prevalence of asthma and wheezing illness in children and adults, it appears that the global prevalence of asthma ranges from 1% to 18% of the population in different countries (GINA, 2008).

So, it is important to assess accurately the impact of such a wide spread illness and its treatment regarding efficacy and safety.Inhaled glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma. Studies demonstrated their efficacy in reducing asthma symptoms, improving quality of life, improving lung function, decreasing airway hyper responsiveness, controlling airway inflammation, reducing frequency and severity of exacerbations and reducing asthma mortality. However, they do not cure asthma, and when they are discontinued deterioration of clinical control follows within weeks to months in proportion of patients (GINA, 2008)

Inhaled corticosteroids have been used for the treatment of asthma in children for more than 20 yr. During this time, a substantial

number of studies have been performed evaluating the safety and efficacy of this therapy. Generally, the results have been reassuring. Inhaled corticosteroids have a marked effect on both the immediate and the long-term aims of asthma therapy (Pederson, 2001). However concern about the potential for systemic adverse events, including linear growth and suppression of adrenal glands, has resulted in reluctance of many physicians and parents to use ICS (Altintas etal., 2005).

In the current case-control study we evaluated the long term effects of inhaled corticosteroids (ICS) e.g. budesonide and beclomethason propionate on growth and serum cortisol level as an indicator of adrenal function.

The research study included anthropometric measurements and serum cortisol level in two groups of asthmatic children, group1 (30 asthmatic patients on ICS) and group 2 (33 asthmatic patients not received ICS). It was found that there is no significant difference in anthropometric measurements and serum cortisol level between the two groups; these results support the safety of ICS on growth. More over, we found that the height of group 2 (children not on ICS) are shorter than group 1 (patients on ICS) .

These come in accordance with Allen 2006, who concluded that avoidance of inhaled corticosteroid therapy has been observed to lead to poorer asthma control, poorer growth as result of poorer asthma control, increased morbidity and hospitalizations, and more frequent need for courses of treatment with systemic corticosteroids .This finding supports the recent studies in which impaired growth was not noticed in asthmatic children receiving ICS in doses that have been considered safe.

Agertoft and Pederson 2000, reported that growth rates were significantly reduced during the first years of budesonide treatment. However these changes in growth rate were not significantly associated with adult height . Children with asthma who received long-term ICS attain normal adult height. Growth deceleration of asthmatic children on maintenance ICS is compensated for after the first 12 monthes of treatment (Anthracopoulos etal., 2007).

The research results also regarded a significant difference between children on ICS receiving 100 µg and those using a dose >100 µg regarding hip and chest circumferences with increases of the used dose. This come in accordance with the result of Zeiger and his collegans (Zeiger etal.,1999), where they found that in patients with mild and moderate asthma, low daily doses of around 100 to 200 µg/d of inhaled corticosteroid produce a clinical effect that, in most trials, is better than the effect of any comparator treatment. No adverse effects on growth have been associated with treatment in this dose range and idiosyncratic adverse reactions are rare.

On the other hand, Van Bever et al.1999; Pederson, 2001 and Reilly et al.2001 stated that there was an adverse effect on growth and slowing of linear growth especially when relatively high doses of inhaled corticosteroids are used.

Significance of difference in waist circumference of increasing duration of ICS more than 12 monthes was observed indicaties the tendancy of central obesity among these patients with long term treatment.

In the current study, there is no significant difference in serum cortisol level between both groups meaning that no serious effect

on adrenal glands was observed; which may be due to the conventional doses in these patients. This come in accordance with the study of Breborowicz and Niedziela 2007 where they stated that the use of fluticasone in doses of up to 1,000 microg/day (or the equivalent of budesonide) as long-term treatment of children with severe asthma did not substantially affect their adrenal function.

An evidence-based study was done in Australia, they present the results of the efficacy and safety of different doses of ICS for asthma based on the available evidence, the use of lower doses of ICS would be associated with fewer side effects without loss of efficacy (Powell and Gibson 2003).

There was also no significant effect of the degree of asthma severity on growth or cortisol level. Positive correlation between dose of ICS and chest , hip and waist circumferences indicating tendancy for cented obesity. While, negative correlation was calculated between duration of treatment and subscapular skin fold thickness which mean that with increase duration of treatment there will be loss of upper trunk fat. Also, there was a negative correlation between age of patients and weight, sitting height, triceps and subscapular skin fold indicating that as the age of patients increases there will be affection of weight, body proportions and fat distribution.

However, Priftis and his collegans 2006 in their study concluded that children on long-term treatment with low and moderate doses of inhaled budesonide demonstrated mild biochemical adrenal suppression which was not related to dose or duration of treatment. Although inhaled budesonide treatment may result in growth deceleration, the latter does not predict adrenal suppression. Moreover, the negative influence of inhaled corticosteroids on height velocity reduces as the duration of treatment increases. Thus, inhaled corticosteroids should be used at the lowest effective doses for as long as necessary. Rizzo and Sole' 2006 also, stated that ICS when administered in low doses, they seem to be safe and effective. Patient monitoring allows for early detection of possible side effects associated with ICS.

In conclusion :

Inhaled glucocorticosteroids are the most effective controller therapy, and are therefore the recommended treatment for asthma for children of all ages. Long-term usage of inhaled steroids in conventional doses did not have any important side effects on adrenal functions and we strongly encourage its use in conventional doses as a safe and effective treatment of bronchial asthma in Egyptian asthmatic children. Also children treated with inhaled corticosteroids for a long time should be followed closely with respect to side effects.

References

1-Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma.N Engl J Med. 2000; 343 :332 –336.

2-Global Initiative for Asthma(GINA). Global Strategy for Asthma Management and Prevention. Available at: http://www.ginasthma.org/. Accessed December 4, 2006

3-National Asthma Education and Prevention Program. Expert panel report: guidelines for the diagnosis and management of asthma update on selected

topics—2002. J Allergy Clin Immunol. 2002;110(suppl) :S141 –S219.

4 - Stafford RS, Ma J, Finkelstein SN, Haver K, Cockburn I. National trends in asthma visits and asthma pharmacotherapy, 1978– 2002. J Allergy Clin Immunol. 2003;111 :729 –735.

5- Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma.N Engl J Med. 2000;343 :1064 –1069.

6-Kennis T. Inhaled corticosteroids: the FDA takes another look. Ann Allergy Asthma Immunol.1998;81 :406 –410.

7-Food and Drug Administration. Guidance for industry: orally inhaled and intranasal corticosteroids—evaluation of the effects on growth in children. Available at: www.fda.gov/Cder/guidance/5514fnl.pdf. Accessed March 12, 2007

8- Allen DB**.** Effects of inhaled steroids on growth, bone metabolism, and adrenal function.Adv Pediatr. 2006; 53:101-10.

9-Hiernau J and Tanner JM . Growth and physical studies. In: Human Biology: A guide to field methods. Eds. Weiner J.S., Lourie S.A., IBP. London, Blackwell Scientific Publications. Oxford. U.K.1969.

10- Global Initiative for Asthma(GINA). Global Strategy for Asthma Management and Prevention. Available at: http://www.ginasthma.org/. 2008; page 22-23.

11- Global Initiative for Asthma(GINA). Global Strategy for Asthma Management and Prevention. Available at: http://www.ginasthma.org/. 2008; page 29.

12-Pederson S. Do Inhaled Corticosteroids Inhibit Growth in Children? Am. J. Respir. Crit. Care Med., Volume 164, Number 4, August 2001, 521-535.

13-Altintas DU, Karakoc GB, Can S, Yilmaz M, Kendirli SG. The effects of long term use of inhaled corticosteroids on linear growth, adrenal function and bone mineral density in children. Department of Pediatric Allergy-Immunology, Cukurova University, Adana, Turkey.(2005)

14-Agertoft L and Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. N Engl J Med 2000; 343: 1064-1069.

15-Anthracopoulos MB, Papadimitriou A, Panagiotakos DB, Syridou G, Giannakopoulou E, Fretzayas A, Nicolaidou P, Priftis KN**.** Growth deceleration of children on inhaled corticosteroids is compensated for after the first 12 months of treatment.Pediatr Pulmonol.2007 May; 42(5):465-70.

16-Zeiger RS, Dawson C, Weiss S. Relationships between duration of asthma and asthma severity among children in the Childhood Asthma Management Program (CAMP) J Allergy Clin Immunol 1999; 103: 376-387.

17-Van Bever HP, Desager KN, Lijssens N, et al. Does treatment of asthmatic children with inhaled corticosteroids affect their adult height? Pediatr Pulmonol.1999; 27: 369-'75.

18-Reilly SM, Hambleton G, Adams JE, Mughal MZ. Bone density inn asthmatic

children treated with inhaled corticosteroids. Arch Dis Child. 2001;84:183-4.

19-Breborowicz A, Niedziela M . Adrenal function in children with severe asthma treated with high-dose inhaled glucocorticoids: recommended screening tests in outpatient conditions. J Pediatr Endocrinol Metab. 2007; Jul;20(7):781-9.

20-Powell H and Gibson PG**.** Inhaled corticosteroid doses in asthma: an evidence-based approach MJA 2003; 178 (5): 223-22.

21-Priftis KN, Papadimitriou A, Anthracopoulos MB, Gatsopoulou E, Fretzayas A, Nicolaidou P, Chrousos GP . Neuroimmunomodulation. 2006;13(1):56-62.

22-Rizzo MC, Solé D. Inhaled corticosteroids in the treatment of respiratory allergy: safety vs. efficacy. J Pediatr (Rio J) 2006; Nov;82 Suppl):S198-205.

Date:2 March, 2010