

Effect of Inhaled Steroids on Adrenal Function in Children with Bronchial Asthma

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ABSTRACT

Introduction: In bronchial asthma, regular treatment for more than 4 years with budesonide once daily (200 or 400 mcg) is safe and well tolerated in children from the age of 5 years with newly detected mild persistent asthma. This study was conducted to see the effect of ICS on HPA in children with bronchial asthma who are on prolonged ICS.

Material and methods: We studied 50 diagnosed patients of bronchial asthma who had been on ICS (200 to 800mcg/day) for a minimum period of 3 months. All patients were assessed for adrenal insufficiency on clinical basis including history, examination and baseline investigations. Adrenal function assessment of these patients was done by low dose ACTH stimulation test.

Results: 50 patients were included in the study (27 males, 23 females). The mean age of patients was 7.5 years (range 2 to 14 years, SD 2.86.) 42 patients (84%) had mild persistent bronchial asthma & 8 patients (16%) had moderate persistent bronchial asthma. The daily inhaled budesonide dose received by our patients was 200 µg in 12 patients, 400 µg in 35 patients, 600 µg in 1 patient and 800 µg in 2 patients. Mean basal cortisol level in our patients was 19.1 µg/dl ± 3.63 (R 11-28). Post ACTH stimulation, mean cortisol levels rose to 24.3 µg/dl ± 4.17 (R 14-36) at 30 minutes and 24.5 µg/dl ± 4.24 R (14-37) at 60 minutes. On low dose ACTH stimulation testing, we documented adrenal insufficiency in 3 patients and no insufficiency was found in 47 patients. However, none of the patients with documented biochemical adrenal insufficiency had any clinical features of adrenal insufficiency.

Conclusion: There was no correlation between cumulative dose of ICS received, duration of ICS treatment & 30 minute cortisol level after ACTH stimulation.

Keywords: Inhaled Steroids, Adrenal Function, Children with Bronchial Asthma

INTRODUCTION

Bronchial asthma is a chronic inflammatory disease of the airways characterized by Bronchial hyperreactivity and a variable degree of airway obstruction¹. It is one of the most important

diseases of childhood causing substantial morbidity². It is diagnosed on the basis of the clinical history, physical examination, and pulmonary function tests, including reversibility testing and measurement of bronchial reactivity¹. Global Initiative for Asthma (GINA) guidelines report that the prevalence of asthma is estimated to be 1% to 18%³. Although inhaled corticosteroids (ICS) are highly effective in the treatment of asthma, their use has been limited because of serious systemic side effects including

suppression of linear growth and hypothalamic pituitary adrenal axis suppression⁴. Regular treatment for more than 4 years with budesonide once daily (200 or 400 mcg) is safe and well tolerated in children from the age of 5 years with newly detected mild persistent asthma⁵. Patients requiring higher doses, which are not licensed, should be referred to a specialist. This is particularly important in a minority of children whose parents may adjust doses upwards or remain highly compliant with treatment recommendations over long periods of time. Only 40-50% of patients are still taking the prescribed dose of ICS after 6 months of treatment⁶, potentially biasing measures of their long-term effects⁷. Clinical trials demonstrate that ICS may cause suppression of the hypothalamic pituitary adrenal (HPA) axis⁸ and adrenal suppression may occur with increasing doses⁹. The HPA axis plays an important role in the maintenance of basal and stress related homeostasis. Plasma cortisol secretion follows a circadian pattern with the highest considerations being seen in the morning. A single estimation of the 08:00 hour serum cortisol concentration reflects endogenous activity of the hypothalamo-pituitary-adrenal axis. The cortisol response to insulin induced hypoglycemia has been validated against the response to surgical stress and is one of the most valuable tests of adrenal insufficiency (gold standard). Unfortunately, it is both unpleasant and potentially dangerous, so there remains a need for a simple, safe, and reliable screening test. The standard short Synacthen test (SSST), in which a pharmacological dose of adrenocorticotrophic hormone (ACTH) is given intravenously, directly measures adrenal reserve. It is also thought to assess hypothalamo-pituitary adrenal function indirectly, because chronic ACTH deficiency leads to a quiescent adrenal gland and therefore to an inadequate cortisol response to exogenous ACTH. The peak serum cortisol concentration obtained 30 minutes after the SSST has been shown to correlate with that obtained after insulin induced hypoglycemia. ACTH can be given as high dose (250mcg/m²) or low dose (1mcg/m²)¹⁰. In a meta-analysis of studies comparing low dose (LDT) and high

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dose test (HDT), it was shown that at a specificity of 95%, both tests have similar sensitivities for diagnosis of secondary adrenal insufficiency (AI) (57% and 61% respectively) and a sensitivity of 97% for HDT for diagnosis of primary AI¹¹. Review of nine studies showed a significantly higher sensitivity and somewhat lower specificity for LDT, with a better accuracy of 90.1% (versus 83.9% for HDT)¹¹.

This study was conducted to see the effect of ICS on HPA in children with bronchial asthma who are on prolonged ICS.

MATERIAL AND METHODS

This study was conducted in department of Paediatrics and Neonatology at Sher-I-Kashmir Institute of Medical Science (SKIMS) Soura, Srinagar and SKIMS Medical College Bemina Srinagar. We studied 50 diagnosed patients of bronchial asthma who had been on ICS (200 to 800mcg/day) for a minimum period of 3 months from July 2016 to June 2018. Adrenal function assessment of these patients was done by low dose ACTH stimulation test.

Inclusion criteria

1. Children with persistent bronchial asthma who were on inhaled steroids for minimum period of 3 months were taken for study.

Exclusion criteria

Following types of patients were not included in the study;

1. Children known to have HPA axis suppression.
2. Children with untreated hypothyroidism/liver disease.
3. Children being treated with Phenytoin, Phenobarbitone, Rifampicin.
4. Children with Addison's disease.

All the patients' records including history, physical examination, investigations and treatment were recorded on a proforma sheet and reviewed. Thyroid function assessment was done and patients of hypothyroidism were excluded from the study. All patients were assessed for adrenal insufficiency on clinical basis including history, examination and baseline investigations. Baseline liver function test was done and patients with liver disease were not taken for study. All patients were called at 8 am in morning. Under all aseptic precautions an intravenous cannula was inserted and a sample for basal cortisol level collected. ACTH injection was given at a dose of 1mcg/1.73m² and repeat samples were collected at 30 and 60 minutes. We did a low dose ACTH stimulation test in our study as low dose ACTH stimulation test is more sensitive than high dose ACTH stimulation test. Blood samples were preserved at a temperature of -20 degree Celsius. Serum cortisol estimation was done by Chemiluminescence method. A normal response to the ACTH test was defined as a peak serum cortisol of >500 nmol/l (>18mcg/dl) and/or incremental concentration of >200 nmol/l (>7mcg/dl).¹⁴

STATISTICAL ANALYSIS

values of cortisol were entered in a spreadsheet (Microsoft excel) and then exported to data editor of SPSS version 20.0 (SPSS Inc, Chicago, Illinois, USA). Continuous variables were expressed as mean \pm SD and categorical

variables were expressed as frequencies and percentages. Frequency distribution tables, bar and pie charts were used for data presentation. Karl Pearson's correlation coefficient and scatter plots were employed to establish correlation between various variables. Chi square test was used to draw correlation between dose and duration of ICS with peak cortisol levels. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 50 patients were included in the study. These included 27 males and 23 females (male: female = 1:1.17). The mean age of patients (Table 1) in our study group was 7.5 years (range 2 to 14 years, SD 2.86). In our study 42 patients (84%) had mild persistent bronchial asthma & 8 patients (16%) had moderate persistent bronchial asthma. None of the patients had severe persistent bronchial asthma. The daily inhaled budesonide dose received by our patients was 200 μ g in 12 patients, 400 μ g in 35 patients, 600 μ g in 1 patient and 800 μ g in 2 patients. Our patients had been on inhaled steroids for a minimum of 3 months (range 3 to 9 months, SD 1.68) as is shown in Table 2. Mean basal cortisol level in our patients was 19.1 μ g/dl \pm 3.63 (R 11-28). Post ACTH stimulation, mean cortisol levels rose to 24.3 μ g/dl \pm 4.17 (R 14-36) at 30 minutes and 24.5 μ g/dl \pm 4.24 R (14-37) at 60 minutes (Table 3).

On low dose ACTH stimulation testing, we documented adrenal insufficiency in 3 patients and no insufficiency was found in 47 patients. However, none of the patients with documented biochemical adrenal insufficiency had any clinical features of adrenal insufficiency.

Age (years)	Male		Female	
	No.	%age	No.	%age
< 5	3	11.1	4	17.4
5-10	16	59.3	14	60.9
10-15	8	29.6	5	21.7
Total	27	100	23	100

Table-1: Age and gender distribution of study patients

Duration (Months)	Frequency	Percentage
3-4 Months	9	18
5-6 Months	22	44
7-8 Months	15	30
\geq 9 Months	4	8
Total	50	100

Mean \pm SD (Range)=6.1 \pm 1.68 (3-9)

Table-2: Showing duration of inhaled steroids in study patients

	N	Pearson Correlation (r - value s)	P-value
Dose-30 Min Cortisol	50	-0.239	0.095
Duration-30 Min Cortisol	50	-0.243	0.089

Table-3: Showing correlation of cumulative ICS dose and Duration of dose (Months) with 30 minute cortisol level after ACTH stimulation

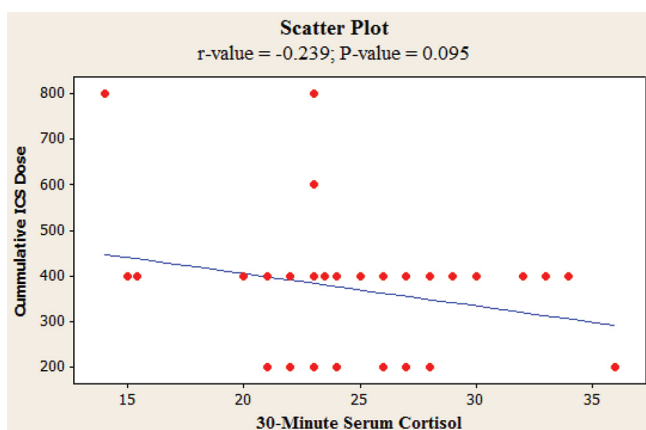


Figure-1: Scatter plot showing correlation of cumulative inhaled steroid dose and 30 minute cortisol level after ACTH stimulation

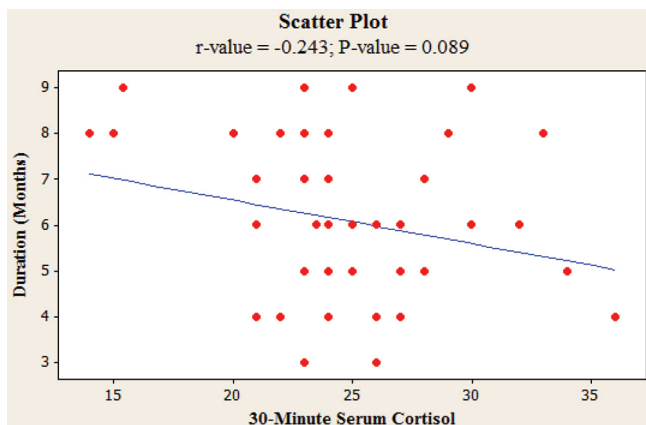


Figure-2: Scatter plot showing correlation between duration of inhaled steroids with 30 minute cortisol level after ACTH stimulation.

There was no correlation between cumulative dose of ICS received, duration of ICS treatment & 30 minute cortisol level after ACTH stimulation (Table 3, Figure 1, Figure 2)

DISCUSSION

Inhaled corticosteroids (ICS) have become widely recognized as the preferred therapeutic modality for persistent asthma¹². At doses recommended for the majority of asthmatic children, a satisfactory safety profile has been established over 3 years of use. Although some concerns remain, both studies and experience show that serious steroid side effects are unusual. At high doses, oral candidiasis may arise¹³ and ICS use has also been linked with effects on growth, HPA axis function and the eyes. Clinical trials demonstrate that ICS may cause suppression of the HPA axis⁸ and adrenal suppression may occur with increasing doses⁹. Even in children whose growth does not appear to have been affected, adrenal suppression cannot be ruled out¹¹. Currently, no study can provide a good basis for practice recommendations however HPA axis evaluation may be performed by specialists using measures of spontaneous cortisol secretion. The evidence for hypothalamic pituitary adrenal suppression by inhaled corticosteroids has been found to be conflicting. Leonard B et al¹⁴ proposed a method of evaluating the function of adrenal cortex for screening tests which seems to recognize all required parameters. Using this method it is possible

to evaluate the basic glucocorticoid function of adrenal gland using basal cortisol levels as well as adrenal reserve evaluation after Synacthen stimulation.

Our study was designed as a prospective study. We enrolled 50 diagnosed patients of bronchial asthma who were put on inhaled steroids. All patients were on inhaled budesonide with dose ranging from 200 to 800mcg/day. None of our patients was on oral steroids during the study period. All patients were followed for a minimum of 3 months and then adrenal function assessment was done by low dose ACTH stimulation test. Our study included children in the age group of 2 to 14 years with mean Age of 7.5 ± 2.86 years. In our study 54% were males and 46% were females. A minimum duration of 3 months of steroid inhalation was taken as an inclusion criterion. In our study patients were on inhaled steroids for a duration of 3 to 9 months with a mean duration of 6.1 months. In our study mean basal cortisol level was found to be 19.1 ± 3.63 mcg/dl (11-28 μ g/dl). At 30 minute mean cortisol level was found to be 24.3 ± 4.17 mcg/dl (14-36mcg/dl). At 60 minutes mean cortisol level was found to be 24.5 ± 4.24 mcg/dl (14-37 mcg/dl). In our study adrenal suppression was found in 6% of patients. This adrenal insufficiency was only biochemical, since none of these patients presented with symptomatic adrenal insufficiency during stress conditions by the time of present study, suggesting that adrenal hyporesponsiveness is not clinically significant. The method of assessment used in our study (low dose ACTH) has

higher sensitivity rather than a high specificity and therefore false positives cannot be ruled out⁹. There was no correlation between dose and duration of inhaled steroids with 30 minute cortisol levels ($P > 0.05$). It is consistent with the study conducted by Bacharier LB et al¹⁴ who also found no significant correlation ($P = 0.14$) between cumulative inhaled steroid dose and serum cortisol at 36 months of follow up. Thus we can say that ICS are a very safe modality of treatment in bronchial asthma, with a very good safety profile & no significant adverse effect on the HPA axis.

CONCLUSION

Our results are in accord with earlier studies showing efficacy and safety of inhaled steroids at recommended doses. Adrenal reserve was decreased in 6% of patients which was statistically insignificant. There was no correlation between dose and duration of inhaled steroids with adrenal insufficiency.

REFERENCES

1. Perrin C. White secondary and tertiary adrenal insufficiency : Kliegman, Stanton, St Geme, Schor; in: Nelson Textbook of Pediatrics 20th edition vol 3; Elsevier;P 2711
2. Arztliches Zentrum für Qualität in der Medizin (ed.): Nationale Versorgungs-Leitlinie Asthma bronchiale (www.asthma.versorgungsleitlinien.de). DtshArztebl2005,1 02(40):A273.
3. Global Initiative for asthma: Global strategy for asthma management and prevention, Revised2020. <http://www.>

- ginaasthma.com.
4. Buhl R, Berdel D, Criece C-P, Gillissen A, Kardos P, Kroegel C et al. Leitlinie zur Diagnostik und Therapie von Patienten mit Asthma. *Pneumologie* 2006; 60: 139-83.
 5. Blodgett FM, Burgin L, Lezzoni D, Gribetz D, Talbot NB. Effects of prolonged corticosteroid therapy on the statural growth, skeletal maturation and metabolic status of children. *N Engl J Med* 1956; 254: 636-641
 6. Sheffer AL, Silverman M, Woolcock AJ, Diaz PV, Lindberg B, Lindmark B. Long-term safety of once-daily budesonide in patients with early-onset mild persistent asthma: results of the Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study. *Ann Allergy Asthma Immunol* 2005;94:48-54.
 7. Jonasson G, Carlsen KH, Mowinckel IP. Asthma drug adherence in a long term clinical trial. *Arch Dis Child* 2000;83:330-333.
 8. Wothers OD, Allen DB. Inhaled corticosteroids, growth, and compliance. *N Engl J Med* 2002;347:1210-1211.
 9. Sim D, Griffiths A, Armstrong D, Clarke C, Rodda C, Freezer N. Adrenal suppression from high-dose inhaled fluticasone propionate in children with asthma. *Eur Respir J* 2003;21:633-636.
 10. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. *Arch Intern Med* 1999;159:941-955.
 11. Stewart PM, Corrie J, Seckl JR, Edwards CPW, Paadfield FL. A rational approach for assessing the hypothalamo-pituitary-adrenal axis. *Lancet* 1988;i:249-51
 12. Rhodes HL, Thomas P, Sporik R, Holgate ST, Cogswell JJ. A birth cohort study of subjects at risk of atopy: twenty-two-year follow-up of wheeze and atopic status. *Am J Respir Crit Care Med* 2002;165:176-18
 13. Leonard B, Bacharier, MD; Hengameh H, Raissy, PharmD, Laura Wilson, ScMs; Bennie McWilliams, MD; Robert C. Strunk, MD; and H. William Kelly, PharmD Long-Term Effect of Budesonide on Hypothalamic-Pituitary-Adrenal Axis Function in Children with Mild to
 14. Moderate Asthma *PEDIATRICS* Vol. 113 No. 6 June 2004
 15. Randell TL, Donaghue KC, Ambler GR, Cowell CT, Fitzgerald DA, Van Asperen PP. Safety of the newer inhaled corticosteroids in childhood asthma. *Paediatr Drugs* 2003;5:481-504

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