

Effects of nebulized corticosteroids therapy on hypothalamic–pituitary–adrenal axis in young children with recurrent or persistent wheeze

Cetinkaya F, Kayiran P, Memioglu N, Tarim OF, Eren N, Erdem E. Effects of nebulized corticosteroids therapy on hypothalamic–pituitary–adrenal axis in young children with recurrent or persistent wheeze. *Pediatr Allergy Immunol* 2008.

© 2008 The Authors

Journal compilation © 2008 Blackwell Munksgaard

Inhaled corticosteroids (ICS) are preferred drugs for the long-term treatment of all severities of asthma in children. However, data about the safety of ICS in infants is lacking. So, it is essential to do further clinical studies to examine the safety and efficacy of ICS in this population. In this study, the effects of nebulized budesonide and nebulized fluticasone propionate suspensions on hypothalamic–pituitary–adrenal axis is examined in infants with recurrent or persistent wheeze. Thirty-one children aged 6–24 months admitted to our hospital between January and December 2005 with symptoms of recurrent or persistent wheeze were included in the study. The patients were randomly allocated to receive 0.25 mg BUD or 0.25 mg fluticasone propionate twice daily for 6 wk and half dose for another 6 wk with a jet nebulizer at home. Blood samples for basal cortisol concentration, adrenocorticotrophic hormone, glucose, HbA1c and electrolytes were obtained at the beginning and at the end of the study. Adrenal function assessment was based on changes in cosyntropin-stimulated plasma cortisol levels. The study was completed with 31 patients, 16 of whom received BUD and 15 FP. All patients except one had plasma cortisol concentrations above 500 nmol/l (18 µg/dl) or had an incremental rise in cortisol of > 200 nmol/l after stimulation. Although nebulized steroids seem to be safe in infancy, we recommend that adrenal functions should be tested periodically during long-term treatment with nebulized steroids.

Feyzullah Cetinkaya¹, Petek Kayiran¹, Nihal Memioglu¹, Omer Faruk Tarim², Nezaket Eren¹ and Ela Erdem¹

¹Sisli Etfal Education and Research Hospital, Istanbul,

²Uludag University School of Medicine, Department of Paediatric Endocrinology, Bursa, Turkey

Key words: asthma; corticosteroids; budesonide; fluticasone propionate; hypothalamic–pituitary–adrenal

Feyzullah Cetinkaya, Atakoy 7-8 kisim D:33, A girisi No:8, 34750 Istanbul, Turkey
Tel.: +90 212 219 38 87
Fax: +90 212 240 29 91
E-mail: feyzulkaya@mynet.com

Accepted 4 January 2008

The aims of asthma management are the control of symptoms, prevention of exacerbations and the achievement of best possible pulmonary function with minimal side effects due to drugs (1). To achieve this goal, inhaled corticosteroids (ICS) are preferred for the long-term treatment of all severities of persistent asthma in children of all ages (2). However, ICS, particularly at high doses, are associated with systemic side effects such as suppression of growth and hypothalamic–pituitary–adrenal (HPA) axis (3). Although inhaled steroids are commonly used

in all age groups there are only a few published studies of adrenal function in children younger than 2 yr of age (4, 5). The objective of this study was to assess the effects of nebulized budesonide and nebulized fluticasone propionate suspensions on HPA axis in infants with recurrent or persistent wheeze.

Materials and methods

Thirty-seven children aged 6–24 months admitted to our hospital between January and December

2005 with at least two documented episodes of wheeze and cough within the last 4 wk were included in the study. Children with known causes of wheezing such as congenital heart diseases, cystic fibrosis and gastroesophageal reflux were excluded from the study. None of the children had been receiving any kind of glucocorticoids before. At the beginning of the study, anthropometric measurements were made, blood pressure was measured and blood samples were taken to measure total serum IgE levels. The patients were randomly allocated into one of the two study groups according to their hospital admission order. The first group (BUD group) received 0.25 mg budesonide twice daily for 6 wk and half dose for another 6 wk with a jet nebulizer (Omron CX3) at home, and the second group (FP group) received 0.25 mg fluticasone propionate twice daily for 6 wk and half dose for the same period. The patients were given nebulized salbutamol as required. Blood samples for basal cortisol concentration, adrenocorticotrophic hormone (ACTH), glucose, HbA_{1C} and electrolytes were obtained at the beginning and at the end of the study between 8:00 and 9:00 hours before breakfast.

At the end of 3 months treatment, adrenal functions of the patients were assessed by cosyntropin-stimulated plasma cortisol levels. For this, a bolus injection of 10 µg cosyntropin (a synthetic corticotropin) was given intravenously and blood samples were obtained at 0, 30 and 60 min for the measurement of serum cortisol concentration. Patients with both a basal plasma cortisol concentration of at least 100 nmol/l and an ACTH-stimulated plasma cortisol concentration that was at least 500 nmol/l or a plasma cortisol that increased by at least 200 nmol/l above the basal concentration after stimulation were defined as having 'normal' adrenal function (6–8). Blood samples for serum ACTH and cortisol levels were also taken in the morning (between 8.00 and 9.00) when the children were fasting for at least 8 h and measured with chemiluminescent immunometric assay (Immulin 2000 analyzer; DPC, Los Angeles, CA, USA). At the end of 3 months treatment period anthropometric measurements were repeated.

The study protocol was approved by the institutional ethics committee.

Statistical analyses

Comparisons between the groups were made with Mann–Whitney *U*-test, Wilcoxon signed ranks test and chi-Squared test. *p* value of <0.05 was accepted as statistically significant.

Table 1. Gender, age, height, weight and wheezing period in BUD and FP groups at the beginning of the study

	FP group	BUD group	<i>p</i>
Gender			
Female	4	7	
Male	11	9	
Initial age (month, mean ± s.d.)	11.00 ± 5.58	9.12 ± 3.09	0.496
Weight (g, mean ± s.d.)	9400.00 ± 2150.18	1093.3 ± 2013.90	0.088
Height (cm, mean ± s.d.)	71.6 ± 9.17	68.6 ± 5.4	0.452
Wheezing period (month, mean ± s.d.)	4.23 ± 4.31	2.90 ± 2.01	0.808
Total IgE (IU/ml)	15.44	23.24	0.024
HbA _{1C} (%)	5.03 ± 0.78	5.37 ± 0.48	0.259

Results

The study was completed with 31 patients 16 of whom received BUD and 15 FP. Six of the patients were excluded from the study because of irregular visits. Both of the groups were comparable at the beginning of the study in terms of mean ages, body weights, familial atopy history, pre-treatment mean serum cortisol, ACTH and HbA_{1C} levels (Table 1). The mean period for wheezing before the treatment was 4.23 months in FP group and 2.90 months in BUD group (*p* > 0.05). Total IgE levels were also similar in both groups (15.44 kIU/l in FP group 23.24 kIU/l in BUD group (*p* > 0.005) (Tables 1 and 2).

All patients except one from BUD group had plasma cortisol concentrations above 500 nmol/l or had an incremental rise in cortisol of ≥200 nmol/l after induction. Plasma cortisol concentrations of this patient from BUD group was as follows; 0 min = 173 nmol/l, 30 min = 361 nmol/l, 60 min = 292 nmol/l. After decreasing the budesonide dose gradually in 1 month the induction test was repeated. In the second test, although ACTH-stimulated plasma cortisol concentration was found to be above 500 nmol/l, basal plasma concentration was ≤ 100 nmol/l. The pre-treatment mean cortisol level was 258.5 nmol/l in FP group and 379.5 nmol/l in BUD group (Table 2) (*p*: 0.027).

Table 2. Pre- and post-treatment serum cortisol and ACTH levels in FP and BUD groups

	FP	BUD	<i>p</i>
Pre-treatment ACTH	19.0 ± 11.6	17.3 ± 11.7	0.684
Post-treatment ACTH	25.35 ± 14.62	23.92 ± 10.27	0.588
Pre-treatment cortisol	258.5 ± 191.8	379.5 ± 309.5	0.027
Post-treatment cortisol (0 min)	321.8 ± 191.0	237.8 ± 98.4	0.323
Post-treatment (30 min)	751.0 ± 106.1	658.2 ± 201.6	0.173
Post-treatment (60 min)	834.0 ± 146.4	771.0 ± 237.4	0.621

ACTH, adrenocorticotrophic hormone.

and pre-treatment mean ACTH level was 19 pg/ml in FP group and 17.37 pg/ml in BUD group (Table 2) ($p = 0.684$).

Pre-test morning mean serum cortisol level was 321.8 nmol/l in FP group, and 237.8 nmol/l in BUD group ($p > 0.05$) after 3 months treatment (Table 2). Serum cortisol levels were comparable between groups after the stimulation test although cortisol levels on 30 and 60 min were insignificantly higher in the FP group than the BUD group ($p > 0.05$). Pre- and post-treatment serum ACTH levels were similar in both groups ($p > 0.05$) (Table 2).

On the other hand, the mean pre-treatment morning cortisol level was lower in the FP group than the BUD group ($p < 0.05$) (Table 2). However, the difference in ACTH levels between the groups was insignificant ($p > 0.05$). Serum HbA_{1C}, sodium, chloride and potassium levels and weight and height gains were similar in both groups.

Discussion

The current asthma management guidelines emphasize the importance of early intervention with ICS as first-line anti-inflammatory therapy in children and adults (2). However, with more frequent use of these drugs, an increasing awareness has been reported regarding their adverse effects (9–11). Clinical adrenal insufficiency with ICS has been reported by some authors (12, 13). Patel et al. (14) have reported a case series illustrating the occurrence of clinically significant adrenal insufficiency in asthmatic children using ICS. Priftis et al. (15) suggested that long-term treatment of asthmatic children with low and moderate doses of inhaled budesonide might result in mild adrenal suppression that cannot be predicted by growth deceleration.

Inhaled corticosteroids have generally been administered to young children by a pressurized metered dose inhaler plus a spacer for the concerns of safety and effectiveness raised by pediatricians about nebulized corticosteroid treatment. However, it was shown that in children with asthma, jet nebulizers deliver approximately 25% of the labeled budesonide dose to the patient; 25% of the remaining dose is delivered to the ambient air, and 50% of the dose stays in the nebulizer (16). In a study performed in 3- to 6-yr-old children with asthma, the total systemic availability (pulmonary plus oral) of budesonide inhalation suspension by a jet nebulizer was found to be approximately 6% of the labeled dose (17). The peak plasma concentration of budesonide occurs approxi-

mately 10–30 min after the start of nebulization in children and adults (18).

Since inhaled forms of corticosteroids have been given to the market long ago, most of the studies related to ICS have also been done with inhaled forms of the drugs (19). There are only a few studies with inhalation suspension of ICS (17). Berger et al. (4) compared the safety of budesonide inhalation suspension with placebo in 141 infants 6–12 months of age with mild to moderate persistent asthma or recurrent wheeze and found that the response to cosyntropin stimulation was similar in budesonide inhalation suspension and placebo groups. In our study, neither BUD nor FP led to clinical and laboratory findings of adrenal insufficiency in any of our patients. Adrenal functions have been evaluated conventionally with high dose ACTH tests, by measuring basal concentrations of plasma cortisol in the morning, or by determining cortisol excretion in the urine. Although there is still uncertainty about what is the most appropriate test for assessment of the integrity of the HPA axis, according to some authors, low dose ACTH tests ($0.5 \mu\text{g}/1.73 \text{ m}^2$) are more sensitive than conventional tests in detecting mild adrenal suppression (20, 21). Abdu et al. (22) compared cortisol responses to the 1 and 250 μg ACTH tests and to the insulin tolerance test in a series of 64 patients with pituitary diseases of various types and found the low dose test to be superior to the 250 μg ACTH test. In contrast, Mayenknecht et al. (23) claimed that the low dose (1 μ) test is not more sensitive than the standard high dose (250 μg) test. In our study, we used 10 μg ACTH which has been suggested to give better results than 250 μg cosyntropin in the assessment of suspicious adrenocortical dysfunction (24) and found that the mean cortisol levels at 60 min were higher than at 30 min in the study population. Fluticasone propionate at a total daily dose of 200 μg is accepted to be safe in children (25). However, in a meta-analysis, Lipworth (9) has reported that fluticasone propionate exhibits greater dose-related systemic bioactivity compared with other available ICS, particularly at doses above 0.8 mg/day. Contrary to this, Kannisto (20), using low dose ACTH test reported that, FP dose of 200 $\mu\text{g}/\text{day}$ caused less adrenal and growth suppression than did a BUD dose of 400 $\mu\text{g}/\text{day}$. In our study, the mean morning serum cortisol levels were significantly lower in FP group than BUD group ($p = 0.027$). As none of the patients had been given any form of corticosteroids before and pre-test and post-test cortisol levels are comparable in both groups, we think these results are coincidental in FP group

with small number of patients. Although the size of the study population is adequate for the methods of statistical analyses utilized in this study, the low number of patients is a limitation.

Although, a period of 3 months seems too short to evaluate the growth rate in children, all of our patients from both groups showed expected growth rate according to our standards.

In conclusion, these data suggest that, at therapeutic dosages for 3 months, inhaled nebulization solutions of corticosteroids do not seem to suppress the HPA axis in young children, but children especially those treated with high doses of inhaled steroids for long-term periods should be followed with screening tests for the functions of HPA axis.

References

- Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention Revised (2002). NHLBI/WHO Workshop Report. Bethesda, MD: National Institutes of Health, National Heart, Lung, and Blood Institute, 2002. NIH publication No. 02: 36–59.
- National Institutes of Health, National Heart, Lung, and Blood Institute. National asthma education and prevention programme. Expert panel report: guidelines for the diagnosis and management of asthma update on selected topics 2002. *J Allergy Clin Immunol* 2002; 110: S142–219.
- VERBERNE AA, FROST C, DUIVERMAN EJ, GROL MH, KERREBIJN KF. Addition of salmeterol versus doubling the dose of beclomethasone in children with asthma. *Am J Respir Crit Care Med* 1998; 158: 213–9.
- BERGER WE, QAQUNDAH PY, BLAKE K, et al. Safety of budesonide inhalation suspension in infants aged six to twelve months with mild to moderate persistent asthma or recurrent wheeze. *J Pediatr* 2005; 146: 91–95.
- WEINBERGER M. Inhaled corticosteroids for infants. *J Pediatr* 2006; 148: 284.
- SPECKART PF, NICHOLOFF JT, BETHUNE JE. 1971 Screening for adrenocortical insufficiency with cosyntropin (synthetic ACTH). *Arch Intern Med* 1971; 128: 761–3.
- ARON DC, BLAKE-TYRREL J. Glucocorticoid & adrenal androgens. In: GREENSPAN FS, BAXTER JD edn 4, eds. *Basic and Clinical Endocrinology*. Norwalk, CT: Appleton & Langhman, 1994: 307–46.
- GRINSPOON SK, BILLER BMK. Laboratory assessment of adrenal insufficiency. *J Clin Endocrinol Metab* 1994; 79: 923–31.
- LIPWORTH BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. *Arch Intern Med* 1999; 159: 941–55.
- TOOGOOD JH. Side effects of inhaled corticosteroids. *J Allergy Clin Immunol* 1998; 102: 705–13.
- PEDERSEN S. State of the art: do inhaled corticosteroids inhibit growth in children? *Am J Respir Crit Care Med* 2001; 164: 521–35.
- MACDESSI JS, RANDELL TL, DONAGHUE KC, AMBLER GR, VAN ASPEREN PP, MELLIS CM. Adrenal crises in children treated with high-dose inhaled corticosteroids for asthma. *Med J Aust* 2003; 178: 214–6.
- DRAKE AJ, HOWELLS RJ, SHIELD JP, PRENDIVILLE A, WARD PS, CROWNE EC. Symptomatic adrenal insufficiency presenting with hypoglycaemia in children with asthma receiving high dose inhaled fluticasone propionate. *BMJ* 2002; 324: 1081–2.
- PATEL L, WALES JK, KIBIRIGE MS, MASSARANO AA, COURIEL JM, CLAYTON PE. Symptomatic adrenal insufficiency during inhaled corticosteroid treatment. *Arch Dis Child* 2001; 85: 330–4.
- PRIFTIS KN, PAPADIMITRIOU A, GATSOPOULOU E, YIALLOUROS PK, FRETZAYAS A, NICOLAIDOU P. The effect of inhaled budesonide on adrenal and growth suppression in asthmatic children. *Eur Respir J* 2006; 27: 316–20.
- SMALDONE GC, CRUZ-RIVERA M, NIKANDER K. In vitro determination of inhaled mass and particle distribution for budesonide nebulizing suspension. *J Aerosol Med* 1998; 11: 113–25.
- AGERTOFT L, ANDERSEN A, WEIBULL E, PEDERSEN S. Systemic availability and pharmacokinetics of nebulized budesonide in preschool children. *Arch Dis Child* 1999; 80: 241–7.
- SZEFLER SJ. Pharmacodynamics and pharmacokinetics of budesonide: a new nebulized corticosteroid: a new nebulized corticosteroid. *J Allergy Clin Immunol* 1999; 104: S175–83.
- CARLSEN KC, STICK S, KAMIN W, CIRULE I, HUGHES S, WIXON C. The efficacy and safety of fluticasone propionate in very young children with persistent asthma symptoms. *Respir Med* 2005; 99: 1393–402.
- KANNISTO S, KORPPI M, REMES K, VOUTILAINEN R. Adrenal suppression, evaluated by a low dose adrenocorticotropin test, and growth in asthmatic children treated with inhaled steroids. *J Clin Endocrinol Metab* 2000; 85: 652–7.
- DICKSTEIN G, SHECHNER C, NICHOLSON WE, et al. Adrenocorticotropin stimulation test: effects of basal cortisol level, time of day, and suggested new sensitive low dose test. *J Clin Endocrinol Metab* 1991; 72: 773–8.
- ABDU TA, ELHADD TA, NEARY R, CLAYTON RN. Comparison of the low dose short synacthen test (1 microg), the conventional dose short synacthen test (250 microg), and the insulin tolerance test for assessment of the hypothalamo-pituitary-adrenal axis in patients with pituitary disease. *J Clin Endocrinol Metab* 1999; 84: 838–43.
- MAYENKNECHT J, DIEDERICH S, BAHR V, PLOCKINGER U, OELKERS W. Comparison of low and high dose corticotropin stimulation tests in patients with pituitary disease. *J Clin Endocrinol Metab* 1998; 83: 1558–62.
- GONZALEZ-GONZALEZ JG, DE LA GARZA-HERNANDEZ NE, MANCILLAS-ADAME LG, MONTES-VILLARREAL J, VILLARREAL-PEREZ JZ. A high-sensitivity test in the assessment of adrenocortical insufficiency: 10 microg vs 250 microg cosyntropin dose assessment of adrenocortical insufficiency. *J Endocrinol* 1998; 159: 275–80.
- GUSTAFSSON P, TSANAKAS J, GOLD M, PRIMHAK R, RADFORD M, GILLIES E. Comparison of the efficacy and safety of inhaled fluticasone propionate 200 micrograms/day with inhaled beclomethasone dipropionate 400 micrograms/day in mild and moderate asthma. *Arch Dis Child* 1993; 69: 206–11.