

Adrenal Function in Children with Asthma and Allergic Rhinitis Treated with Combination of Inhaled and Nasal Corticosteroids

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Introduction: Children with asthma and allergic rhinitis are often treated with a combination of inhaled and nasal corticosteroids. Safety data on this combination treatment in children are not available. This study evaluates adrenal function in children receiving combination therapy with nasal and inhaled corticosteroid using a low-dose adrenocorticotropin (ACTH) test.

Methods: Twelve children aged 6–12 years with severe asthma and allergic rhinitis were given combination therapy with high-dose inhaled HFA-beclomethasone dipropionate (HFA-BDP) (320 µg/day for first 2 months and 160 µg/day thereafter) and flunisolide nasal spray (116 µg/day). A low-dose ACTH test was performed before treatment and 6 months later.

Results: There was no significant change (mean ± SD) in both baseline (7.78 ± 5.34 before treatment and 7.53 ± 4.02 after treatment, $p = 0.42$) and stimulated (22.58 ± 6.97 before treatment and 19.2 ± 3.53 , $p = 0.09$ after treatment) cortisol levels.

Conclusion: Combination therapy with high-dose HFA-BDP and flunisolide nasal spray did not cause suppression of adrenal function in pediatric patients with severe asthma and allergic rhinitis.

Introduction

THE ASSOCIATION OF ASTHMA with allergic rhinitis is common in children.^{1–3} Combination therapy with inhaled and nasal corticosteroids is often prescribed for treatment of these associated conditions. Inhaled corticosteroid therapy can result in some degree of systemic exposure. The assessment of adrenal function in adults receiving combination therapy with inhaled and nasal corticosteroids has suggested the presence of adrenal suppression.⁴ However, similar data on this combination therapy in children is very limited.⁵ There is a concern among practitioners that an increased corticosteroid exposure with combination therapy may potentially cause adrenal suppression and growth retardation.

The goal of our study was to investigate adrenal function in children with asthma and allergic rhinitis receiving therapy with a combination of oral inhaled corticosteroids (ICS) and nasal corticosteroids (NCS).

Materials and Methods

The study was approved by Institutional Review Board (IRB) of Maimonides Medical Center. The design of the study was a prospective, open-labeled, uncontrolled clinical investigation.

Patients with severe persistent asthma with allergic rhinitis were enrolled in the study. The diagnosis and severity of asthma was established by pediatric pulmonologist and was based on NAEPP guidelines.⁶ The diagnosis of allergic rhinitis was established by pediatric allergist and was based on history and symptoms of rhinitis and positive skin testing for seasonal or perennial allergens.⁷ Study patients did not use systemic, inhaled and/or nasal corticosteroids for more than 3 months before enrollment in the study. The ages of the children were between 6 and 12 years and all were able to perform spirometry. Children with any chronic pulmonary disease other than asthma, chronic nonpulmonary illnesses, endocrine diseases, and genetic disorders were excluded from the study.

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Treatment of asthma and allergic rhinitis

All children received beclomethasone dipropionate HFA (HFA-BDP) (Qvar, IVAX/TEVA) 80 µg, four puffs twice a day (640 µg/day) for the first 2 months and 80 µg, two puffs twice a day (320 µg/day) thereafter. The use of a valved holding chamber with mouthpiece was mandatory for the delivery of the ICS. Of note, the doses of HFA-BDP used in the study were somewhat higher than recommended by the manufacturer. This off-label use of the drug was dictated by the severity of asthma symptoms in our patients and was approved by MMC IRB.

Allergic rhinitis was treated with flunisolide (Nasarel, IVAX), 29 µg, two puffs each nostril daily (116 µg/day).

Compliance with medication regimen

All patients underwent follow-up visits with the research team every month. FEV1 was ascertained and empty canisters were counted. The phone calls ensured proper medication use and were conducted weekly during entire study. No emergency asthma visits, which required systemic steroid use, occurred in the study patients.

Outline of the study

After enrollment in the study all patients underwent the following evaluation:

- Height measurement (stadiometer Seca 216).
- FEV1 before bronchodilator.
- Baseline plasma cortisol.
- Stimulated plasma cortisol.

After 6 months of therapy for asthma and allergic rhinitis with the combination of ICS and NCS all measurements were repeated.

Low-dose ACTH test

Low-dose adrenocorticotropin (ACTH) was used for stimulation of cortisol production.

The test was performed between 9 am and 10 am. After the placement of an intravenous catheter a blood sample for basal plasma cortisol was obtained. One microgram of Cortrosyn (Amphostar) was injected intravenously. The blood samples for stimulated cortisol were drawn in 20, 30, and 60 min after injection. A cortisol level of ≥ 14 after ACTH stimulation was considered to be normal.^{8,9}

The preparation of 1 µg Cortrosyn solution was done immediately before the test. In brief, the vial of Cortrosyn (250 µg) was diluted with 1 cc of normal saline (NS) obtained from 50 cc NS bag. A whole dose of Cortrosyn was then injected into the same bag with NS and gently mixed for 3 min. Then 0.2 cc (1 µg) of Cortrosyn solution was obtained from the bag with 1 cc syringe and used for the test.

Statistics

The data was analyzed using Sigma Stat, and graphically represented using SigmaPlot software (Systat Software, Inc., Point Richmond, CA, USA). All values are expressed as mean $\pm$ SD. Significance of differences between the values before and after treatment with corticosteroids was evaluated using two-tailed Student *t* test.

Results

There was no significant change (mean $\pm$ SD) in either baseline (7.78 ± 5.34 before treatment and 7.53 ± 4.02 after treatment, $p = 0.42$) or stimulated (22.58 ± 6.97 before treatment and 19.2 ± 3.53 after treatment, $p = 0.09$) cortisol levels (Fig. 1).

Two-way analysis of variance was used to compare the cortisol levels at baseline and following stimulation with ACTH in the patients before and after treatment with ICS and NCS. This test showed that ACTH stimulation significantly increased ($p < 0.001$) the levels of cortisol, and such an increase was not significantly different in the patients before compared to after the treatment with ICS and NCS.

The stimulated cortisol level was low in two patients before treatment but normal and borderline-normal after treatment (Table 1, boldface values).

There was no change in deviation from mean height percentile (0.034 ± 1.203 before treatment and 0.008 ± 1.04 after treatment, $p = 0.704$) or actual height percentile (51.9 ± 33.4 before treatment and 47.7 ± 33.1 after treatment, $p = 0.91$) in study patients.

FEV1 in study patients significantly increased after therapy ($82 \pm 11\%$ and $90 \pm 8.3\%$, $p = 0.028$) (Fig. 2).

Discussion

There are very limited data available on the safety of combined therapy with ICS and NCS. Sheth et al.⁵ compared baseline and stimulated cortisol levels in patients receiving inhaled fluticasone propionate (FP) versus levels in patients receiving the combination of inhaled and nasal FP. They found that concurrent administration of intranasal FP and orally inhaled FP was not associated with HPA-axis suppression. The authors did enroll children 12–18 years of age in the study, but they did not analyze this subgroup. In addition, the use of the standard ACTH test could significantly reduce the sensitivity of adrenal suppression assessment in their patients. In the study by Wilson et al.,⁴ 12 patients were randomized in blocks to receive two treatment sequences of combinations of nasal placebo with inhaled placebo, nasal placebo with ICS, NCS with inhaled placebo and ICS and

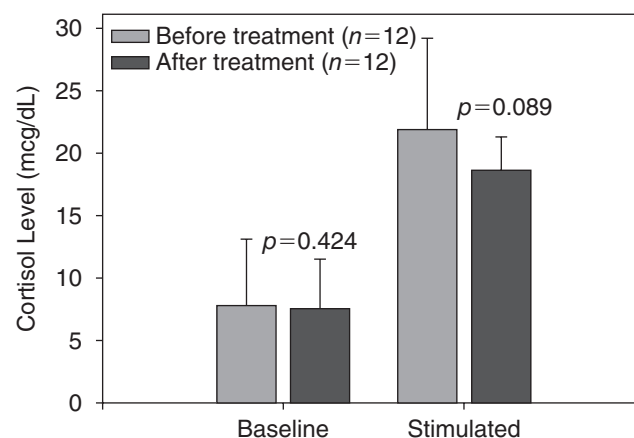


FIG. 1. Cortisol levels in children with asthma before and after treatment with combination of ICS and NCS.

TABLE 1. BASAL AND STIMULATED CORTISOL VALUES IN STUDY PATIENTS BEFORE AND AFTER THERAPY

Before treatment		After treatment	
Basal cortisol	Stimulated cortisol	Basal cortisol	Stimulated cortisol
3.6	22	4.1	17
7.3	31	11	19
5.7	17	5	20
3.9	11	9.4	14
4.1	24	5.2	22
15	29	14	21
5.7	16	4.7	19
2.7	11	4.6	16
6.6	26	2.3	16
7.7	19	7.9	17
21	29	3.2	21
10	29	12	22
7.8 ± 5.3	21.9 ± 7.1	7.1 ± 3.8	18.7 ± 2.6

Value at the bottom of each column is mean ± SD. The bold face values indicate that the stimulated cortisol level was low in two patients before treatment but normal and borderline-normal after treatment.

NCS. Fluticasone propionate and triamcinolone acetonide were given at clinically recommended doses. There were significant differences in serial 24 h and fractionated serum cortisol levels and corrected urinary cortisol excretion between the active treatment groups and placebo. The addition of NCS did not produce further suppression of cortisol levels. No ACTH stimulation test was done. Children were not enrolled in this study.

The limited safety data on the combined use of ICS with NCS in children causes concern in medical practitioners and families of children with asthma and allergic rhinitis.^{10,11}

Both medications used in our study have good safety profiles in children. Use of HFA-BDP was not associated with a decrease in 24-h free urinary cortisol or morning

plasma cortisol.¹²⁻¹⁵ Nayak et al.¹⁶ showed the absence of any difference in baseline and stimulated with low-dose ACTH cortisol level in children with asthma after 12 weeks of therapy with HFA-BDP. In the study by Gale et al.,¹⁷ nasal flunisolide did not cause adrenal suppression in children with allergic rhinitis. The results of our study are reassuring and suggest that combination therapy with the two mentioned above medications most likely does not suppress adrenal function in children despite "off-label" use of high doses of HFA-BDP.

The increase of FEV1 after 6 months of treatment in our study patients was predictable, based on previous studies of HFA-BDP in children with asthma,^{12,13,15,16,18} and is suggestive of good medication adherence in our study population. Adherence was further supported by counting empty canisters and weekly phone calls.

There is no standard approach to the assessment of adrenal function in patients receiving inhaled or nasal corticosteroids. There are several tests, which have been used in the past for the assessment of adrenal function in children. They include morning cortisol, ACTH levels, integrated serial cortisol levels (24 h, or overnight), free urinary cortisol level over 24 h (usually with creatinine correction), ACTH stimulation test, metyrapone test, and insulin tolerance test.

A single morning cortisol level is weakly sensitive due to its wide variations in the same subject. The integrated overnight cortisol measurement is a more reliable test, but it requires multiple blood sampling. The free urinary cortisol over 24 h appears to be practical and reliable, because it provides a global evaluation of the adrenal function; however, obtaining a complete 24-h urine sample in children may be problematic.¹⁰

Insulin-induced hypoglycemia is one of the most reliable tests and considered to be a gold standard test for assessing the HPA axis, but it can be unpleasant to the patient and must be performed by highly experienced personnel because of the risk of profound hypoglycemia.

It has been suggested that the standard (high-dose) ACTH test should be used for the initial assessment of the HPA axis because it is safe, reliable, and easy to perform. Comparison studies have shown it to closely correlate with the insulin tolerance test.¹⁹⁻²¹ However, standard or so called high-dose ACTH test has also been shown to be less sensitive in diagnosing secondary adrenal insufficiency because supraphysiological levels of adrenocorticotropin in the blood may cause adrenal gland overstimulation.²²⁻²⁴ Broide et al.²⁵ assessed the adrenal function of children and adults taking high doses of inhaled budesonide and beclomethasone. Decreased cortisol secretion compatible with mild adrenal insufficiency was detected after stimulation with low-dose ACTH in 16 patients. Nonetheless, all but one of the poor responders to the low-dose ACTH test showed normal stimulation with the standard ACTH test. The low-dose ACTH test has been proposed to be a more physiological stimulatory test with better sensitivity than the standard high-dose test, with a greater ability to uncover mild adrenal insufficiency.²⁶⁻³⁵

Because of this, we chose to use the low-dose ACTH test. This particular test was previously shown to be a reliable tool for the assessment of adrenal function in children receiving inhaled corticosteroids.^{8,9,16,25} Several modifications of the low-dose ACTH test have been previously used by researchers.^{8,9,25-28,35} We chose the 1 µg modification due to its simplicity and proven high sensitivity in assessment of

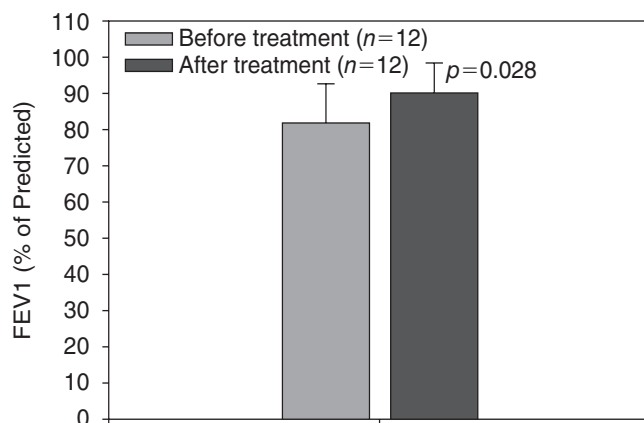


FIG. 2. FEV1 in children with asthma and allergic rhinitis before and after treatment with combination of ICS and NCS.

adrenal function in children.⁹ We adapted the normal levels of stimulated cortisol from the previously published studies, which also used low-dose ACTH stimulation test for the assessment of adrenal function in children.^{8,9} None of our study patients had low stimulated cortisol levels after treatment with combination of ICS and NCS and only one patient had a borderline cortisol level of fourteen.

Our study has certain limitations. Absence of suppression of cortisol production was convincing but was studied in a small group of patients. The *p* value of 0.09 with stimulated cortisol data could suggest a trend toward adrenal suppression after treatment, which potentially could become statistically significant if the power of the study would be increased. However, it is important to recognize that neither of the study patients had lower than a "cut off" stimulated cortisol level, which makes clinically significant adrenal suppression very unlikely. Also, the clinical significance of this level of suppression is very questionable. Compliance monitoring could be further improved with the use of metered dose inhaler counters and canister weighing. Ideally, use of several groups would allow for comparison of patients on just nasal corticosteroids, with those on only oral inhaled corticosteroids, or with those on both.

Overall, we conclude that combination therapy with HFA-BDP used with valved holding chamber and nasal flunisolide did not cause suppression of cortisol secretion in our study patients judged by negative low-dose ACTH stimulation test. These data suggest that this type of combination therapy is unlikely to cause clinically significant adrenal suppression and may be used in children with asthma and allergic rhinitis.

Further studies are recommended to assess the safety of combination therapy with ICS and NCS in children when different medications, doses, and lengths of treatments are used.

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