

Effects of repeated once daily dosing of three intranasal corticosteroids on basal and dynamic measures of hypothalamic-pituitary-adrenal-axis activity

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Background: Intranasal corticosteroids are regarded as the first-line treatment for allergic rhinitis, but few studies have directly compared their systemic effects.

Objective: We sought to compare the hypothalamic-pituitary-adrenal (HPA)-axis suppression with three intranasal corticosteroids in terms of basal and dynamic adrenocortical activity.

Methods: Sixteen healthy volunteers (mean age, 30.7 years) were studied in a single-blind, randomized, four-way crossover study comparing placebo with 200 µg/day fluticasone propionate (FP), 220 µg/day triamcinolone acetonide (TAA), and 336 µg/day beclomethasone dipropionate (BDP). After 4 days of treatment, an overnight urine collection was taken for cortisol and creatinine excretion starting at 10 PM (14 hours after the fourth dose), and blood was taken for serum cortisol at 8 AM (24 hours after the fourth dose) and after stimulation with adrenocorticotrophic hormone (ACTH) (0.5 µg).

Results: For overnight urinary cortisol excretion compared with placebo (20.8 nmol), there was a significant ($p < 0.05$) degree of suppression with FP (11.8 nmol) but not with TAA (16.0 nmol) or BDP (16.5 nmol). In terms of fold difference (95% CI for difference) from placebo, this amounted to 1.75-fold (1.01 to 3.03) for FP (43% suppression), 1.30-fold (0.75 to 2.25) for TAA (23% suppression), and 1.26-fold (0.73 to 2.18) for BDP (21% suppression). There was also a trend towards suppression of overnight urinary cortisol/creatinine excretion, but this was not statistically significant (placebo, 5.2 nmol/mmol; TAA, 5.0 nmol/mmol; BDP, 4.3 nmol/mmol; and FP, 4.3 nmol/mmol). Values for serum cortisol before and after ACTH stimulation showed no significant suppression.

Conclusion: Suppression of overnight urinary cortisol occurred with intranasal FP (43%), TAA (23%), and BDP (21%), although this was only statistically significant with FP. None of the drugs were associated with blunting of the response to ACTH stimulation. Further studies are indicated to establish whether the systemic effects of inhaled and intranasal corticosteroids are additive. (*J Allergy Clin Immunol* 1998;101:470-4.)

Key words: Hypothalamic-pituitary-adrenal axis, cortisol, adrenocorticotrophic hormone, intranasal corticosteroids, fluticasone propionate, beclomethasone dipropionate, triamcinolone acetonide

Allergic rhinitis is a common medical condition causing irritation and impaired quality of life for subjects with the condition. Since their introduction 20 years ago, intranasal corticosteroids have become the first-line treatment of allergic rhinitis.¹ Studies have shown favorable efficacy of intranasal corticosteroids compared with placebo and antihistamines.²⁻⁴

Intranasal corticosteroids have generally been regarded as being safe and free from systemic adverse effects.⁵⁻⁷ Intranasal administration of corticosteroids is associated with a high level of systemic bioavailability, probably because of the abundant vascularity of the nasal mucosa and lipophilicity of modern drugs.⁸ The use of modern aqueous pump sprays is associated with high intranasal deposition,⁹ although this may be partially offset by rapid nasociliary clearance into the throat. Furthermore, there is no first-pass inactivation in the nose, and thus absorption of the unchanged drug occurs directly into the systemic circulation. It is now increasingly recognized with inhaled corticosteroids that detectable systemic activity occurs at doses less than 1000 µg/day,¹⁰ particularly with fluticasone propionate (FP) because of its specific pharmacologic and pharmacokinetic properties.¹¹ The question therefore ensues as to whether the same effects occur with nasal corticosteroids when given in clinically recommended doses.

Hypothalamic-pituitary-adrenal (HPA)-axis suppression is recognized as a sensitive and reproducible marker of the systemic bioactivity of corticosteroids.⁸ Nevertheless, measuring HPA-axis suppression in terms of early morning serum cortisol concentration or urinary cortisol excretion only gives information about the basal endogenous adrenocortical activity. It is also clinically relevant to look at the effect of the cortisol response to adrenocorticotrophic hormone (ACTH) stimulation because this will indicate the degree of dynamic adrenal reserve. In this respect it is known that stimulation with low-dose ACTH (0.5 µg) is a more sensitive means of detection of impaired adrenocortical reserve than the conventional high-dose (250 µg) test in patients receiving long-term inhaled corticosteroids.¹² The 250 µg dose of ACTH

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Abbreviations used

ACTH:	Adrenocorticotrophic hormone
BDP:	Beclomethasone dipropionate
FP:	Fluticasone propionate
HPA:	Hypothalamic-pituitary-adrenal
TAA:	Triamcinolone acetonide

(tetracosactrin) is considered to be supraphysiologic. The 0.5 μg dose is a much better reflection of a physiologic stress response and correlates well with the insulin stress response.¹³ Unfortunately, the ACTH stimulation test is now contraindicated in the UK data sheet (Synacthen, CIBA Laboratories) for allergic or asthmatic patients because of occasional reports of hypersensitivity and fatal anaphylactic reactions. Hence for ethical reasons, at least in the U.K., research studies with ACTH stimulation are not possible in patients with allergic rhinitis.

We present the findings of the first randomized, placebo-controlled study to directly compare the systemic activity of intranasal triamcinolone acetonide (TAA), beclomethasone dipropionate (BDP), and FP in terms of effects on sensitive parameters of basal and dynamic HPA-axis activity, namely overnight urinary cortisol excretion and cortisol response to stimulation with a physiologic dose of ACTH (0.5 μg). This study, however, was not intended to evaluate the relative efficacy of the three treatments.

METHODS

Patients

Sixteen healthy, nonallergic volunteers (nine women and seven men; mean age [SEM], 30.7 [2.7] years) completed the study. All subjects had normal full blood counts and biochemical profiles (including creatinine, urea, electrolytes, and liver function), normal urinalysis, and normal spirometry. In light of the case reports of anaphylaxis in atopic subjects after injection of Synacthen, all volunteers were screened for an atopic history or a positive skin prick test response. Any volunteer with a Grade 1 response or greater (>3 mm) to skin prick testing with house dust mite, grass, or tree pollen allergens was excluded. No subject had previously been treated with inhaled or nasal corticosteroids nor was any subject receiving regular medication. All gave written informed consent, and approval for the study was obtained from the Tayside Medical Ethics Committee.

Study design

A single (investigator), blind, randomized (with Williams Design), four-way, crossover, placebo-controlled design was used. Subjects received four different randomized intranasal treatments with either 55 μg TAA per actuation (Nasacort AQ; Rhone Poulenc Rorer Pharmaceuticals); 50 μg FP per actuation (Flonase, Glaxo Wellcome, Inc.), 84 μg BDP per actuation (Vancenase AQ double strength, Schering Corporation), or placebo. Each treatment was given once daily, two squirts up each nostril, at 8 AM for 4 days. The total daily dose per drug was administered so as to represent the highest recommended dose level (i.e., TAA: 220 $\mu\text{g}/\text{day}$, FP: 200 $\mu\text{g}/\text{day}$, and BDP:

336 $\mu\text{g}/\text{day}$). There was also an initial, nonrandomized, 4-day placebo run-in before the randomized treatment block. The initial nonrandomized placebo was compared with the randomized placebo to assess for any carryover effect within the study. Each of the four randomized treatments were separated by a 7-day washout period.

At the beginning of the trial, the nasal sprays were masked and sealed in envelopes, along with instruction sheets, by a pharmacist to make them investigator blind. Before the study and at each visit, subjects were given detailed instructions by a third party observer in how to use their nasal sprays according to the manufacturer's package insert instructions. Each device was initially primed according to the manufacturer's instructions before first use, and in addition, subjects were instructed to discharge two squirts before each treatment was administered. Subjects received a written instruction sheet to follow while taking their nasal spray at home, and a simple tick chart was used as an aide to compliance.

Measurements

The subjects attended the laboratory at 7:30 AM (i.e., 23½ hours after taking the fourth dose of each study drug). A cannula was inserted into the antecubital fossa vein, and subjects then rested in the supine position for 30 minutes. After the rest period, blood samples were taken for measurement of serum cortisol at 8 AM. ACTH (Synacthen) was diluted to 0.5 $\mu\text{g}/\text{ml}$ by injecting the 250 μg vial into a 500 ml bag of 0.9% saline solution. After mixing, 1 ml aliquots were withdrawn from the bag and used for injection. Subjects received the injection immediately after taking the 8 AM serum sample, and further serum samples were taken after 20 and 30 minutes. Subjects also emptied their bladder at 10 PM on the evening of the fourth day of treatment and collected all overnight voided urine from that time until 7:30 AM the following morning on arrival. After recording the volume, the specimen aliquots were kept for assay of cortisol and creatinine.

Assays

Serum and urinary cortisol were measured by using a commercial radioimmunoassay kit (Immunodiagnostic Systems Ltd.). The coefficient of variation for analytic imprecision within the assay for serum cortisol was 8.1%, and between the assays it was 6.6%. For urinary-free cortisol excretion, the coefficient of variation was 10% within the assay and 5.7% between the assays. Urinary creatinine was measured on a Cobas-bio autoanalyser (Roche Products Ltd.). The coefficient of variation was 1.76% within the assay and 2.93% between the assays. The lower limit for the normal reference range of 8 AM and post-ACTH serum cortisol levels in our laboratory is 150 nmol/L and 500 nmol/L, respectively.

Statistical analysis

The study was designed with a sample size of 16 with 90% power (β -error = 0.1) to detect a 20% difference in overnight urinary cortisol (the primary end point) between treatments, with the α -error set at 0.05 (two-tailed). The peak response to ACTH stimulation was considered to be the higher of the samples taken after 20 and 30 minutes. To normalize its distribution, all data were analyzed by logarithmic transformation. All data were analyzed with a Statgraphics software package (STSC Software Group, Rockville, Md.). Comparisons were made of all three treatments (BDP, FP, and TAA) and both placebos (randomized and nonrandomized) by an overall analysis of variance with subject, treatment, and period as

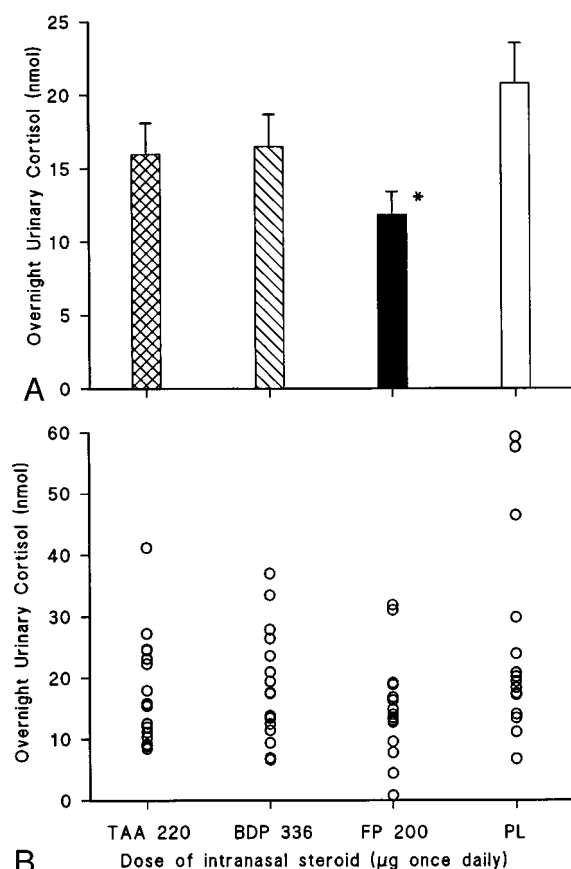


FIG. 1. Geometric mean (and SEM) (A) and individual values (B) for overnight urinary cortisol excretion with intranasal administration of placebo, 220 μ g once daily TAA, 336 μ g once daily BDP, and 200 μ g once daily FP. Percentage suppression for each drug (vs placebo): FP, 43%; TAA, 23%; BDP, 21%. Asterisks denotes significant ($p < 0.05$) difference from placebo. PL, Placebo.

factors. Bonferroni's multiple-range testing was then applied to obviate multiple pair-wise comparisons so as to assess where there were significant differences between treatments and the randomized placebo. The Bonferroni's range test was set with 95% confidence intervals, and therefore any significant differences are only reported at p levels less than 0.05. Also calculated were 95% confidence intervals for the mean treatment differences (vs randomized placebo). Values are given in the text as geometric means and standard errors (SEM).

RESULTS

There was no significant carryover effect between the nonrandomized placebo and the randomized placebo, respectively, with any of the parameters measured (as geometric means $\pm$ SEM) (overnight urinary cortisol, 17.1 ± 2.3 vs 20.8 ± 2.8 nmol; pre-ACTH serum cortisol, 547.5 ± 23.2 vs 574.0 ± 24.3 nmol/L; or post-ACTH, 781.2 ± 32.6 vs 761.0 ± 31.7 nmol/L). The randomized placebo was used for all comparisons with the three active treatments.

Overnight urinary cortisol excretion

Compared with placebo (20.8 ± 2.8 nmol), there was statistically significant ($p < 0.05$) suppression with FP (11.8 ± 1.6 nmol) but not with TAA (16.0 ± 2.1 nmol) or BDP (16.5 ± 2.2 nmol) (Fig. 1, A). This amounted to a 1.75-fold difference (43% suppression) between placebo and FP (95% CI for difference, 1.01 to 3.03). There was a 1.30-fold difference (23% suppression) between placebo and TAA (95% CI for difference, 0.75 to 2.25) and a 1.26-fold difference (21% suppression) between placebo and BDP (95% CI for difference, 0.73 to 2.18). There were no significant differences between the three active treatments. There was also a trend towards suppression of the overnight urinary cortisol/creatinine ratio, but this was not statistically significant (placebo, 5.2 ± 0.5 nmol/mmol; TAA, 5.0 ± 0.5 nmol/mmol; BDP, 4.3 ± 0.4 nmol/mmol; and FP, 4.3 ± 0.4 nmol/mmol). Individual values for overnight urinary cortisol are depicted in Fig. 1, B. This shows that there was considerable variability within individuals in the propensity for suppression.

Pre-ACTH 8 AM serum cortisol

There were no significant differences between placebo (574.0 ± 24.3 nmol/L) and any of the other treatments (TAA, 572.3 ± 24.2 nmol/L; BDP, 590.6 ± 25.0 nmol/L; and FP, 581.9 ± 24.6 nmol/L). There were no patients who had an individual value less than 150 nmol/L for any drug.

Post-ACTH serum cortisol

There were no significant differences between placebo (761.0 ± 31.7 nmol/L) and any of the other treatments (TAA, 767.8 ± 32.0 nmol/L; BDP, 749.6 ± 31.2 nmol/L; and FP, 769.7 ± 32.1 nmol/L). There were no patients who had an individual value less than 500 nmol/L for any drug.

DISCUSSION

Suppression of overnight urinary cortisol occurred with FP (43%), TAA (23%), and BDP (21%), although this was only statistically significant for FP. The presence of detectable adrenal suppression does not necessarily imply that the observed effects are clinically relevant, although it is evident from the scatter plot that individuals differ in their susceptibility to the systemic adverse effects of intranasal corticosteroids. It is important to point out that this degree of suppression would probably not result in an acute adrenal crisis if patients were to abruptly stop their treatment or be exposed to acute stress. The presence of detectable adrenal suppression represents a marker of potential systemic bioactivity, although it may not be possible to extrapolate to effects in other tissues such as bone. It is, however, likely that the effects of intranasal and inhaled corticosteroids would be additive in terms of their combined systemic bioactivity.⁸

Our results with suppression of overnight urinary cortisol are in keeping with other studies, which have shown systemic bioactivity with intranasal FP in terms of

significant effects on serum osteocalcin¹⁴ and blood eosinophil counts.² The fact that intranasal corticosteroids cause detectable systemic activity is not surprising because there is no first-pass inactivation in the nose, resulting in extensive systemic absorption of unchanged active drug.⁸ Whether BDP undergoes partial biotransformation to active and inactive metabolites in the nose (as in the lung) is not clear. We studied healthy volunteers, and it is possible that nasal deposition and bioavailability might be altered in the presence of severe rhinitis because of effects of inflammation and associated secretions. We did not evaluate the efficacy of the intranasal corticosteroids, and it is therefore not possible to draw any conclusions regarding their relative beneficial effects. It is likely that the doses used in this study are on the steep part of the systemic dose-response curve but on the flat part of the efficacy curve. Further dose-ranging studies would be required to properly evaluate therapeutic ratios.

The explanation for the greater systemic activity with FP requires consideration of the different pharmacologic properties of the drugs studied. By using the McKenzie skin vasoconstrictor assay, FP is at least twice as potent as BDP or TAA.^{15, 16} FP also has a much longer receptor residency half-life (11.5 hours) as compared with either TAA (3.9 hours) or beclomethasone 17-monopropionate (8.5 hours).¹⁷ Because of the greater potency and longer receptor half-life of FP, these factors could contribute to more pronounced effects on glucocorticoid receptors in the pituitary and hypothalamus, resulting in HPA-axis suppression.

Each of the drugs were given for 4 days to achieve steady-state levels in the blood. It has been shown that the HPA-axis suppression from steady-state dosing of inhaled FP is greater than that found after single dosing.¹⁸⁻²⁰ The particular pharmacokinetic characteristics of FP, namely the long plasma elimination half-life at 14.4 hours²⁰ and high degree of lipophilicity,²¹ may result in increased accumulation in blood and systemic tissue retention at steady-state. This presumably accounts for the presence of detectable suppression of overnight urinary cortisol 14 hours after the last dose of intranasal FP in this study. Similar differences between FP and other corticosteroids have been observed at steady-state when given by the inhaled route.^{10, 22, 23}

Although the recommended doses of corticosteroids used intranasally for the treatment of allergic rhinitis are small in comparison with those given by an inhaler for the treatment of asthma, the tissue delivery is greater with a nasal aqueous pump spray than with a pressurized metered-dose inhaler.⁹ Indeed, it has been suggested that the nasal bioavailability is at least twice that of lung bioavailability when comparing microgram-equivalent nominal doses given by each route.⁸

It has been previously shown that uncorrected 24-hour urinary cortisol is a more sensitive marker of adrenal suppression than a spot morning 9 AM plasma cortisol level.^{24, 25} McIntyre et al.²⁵ found that overnight urinary cortisol was as sensitive as 24-hour urinary cortisol. It

was therefore not surprising to find that in this study overnight urinary cortisol was more sensitive than spot 8 AM serum cortisol, as has been shown in previous studies from this laboratory with inhaled corticosteroids.^{10, 23}

We performed a low-dose (0.5 µg) ACTH stimulation test to assess dynamic HPA-axis function. This revealed no blunting of the cortisol response for any of the three drugs. Although steady-state drug levels would have been reached in our study, it is possible that an impaired response to ACTH stimulation might have occurred after more prolonged treatment as a consequence of impaired adrenal reserve caused by adrenocortical atrophy. In this respect Broide et al.¹² showed, in a study with patients receiving long-term inhaled BDP and budesonide, that there was a good correlation with the low-dose (0.5 µg) ACTH test and 24-hour urinary cortisol excretion in terms of identifying patients with impaired adrenocortical function. Previous long-term studies with clinically recommended doses of intranasal FP, TAA, and BDP have shown no evidence of HPA-axis suppression in terms of a bolus or 6-hour infusion with high-dose (250 µg) ACTH.^{5, 6, 7} This may reflect the relative insensitivity of the 250 µg dose of ACTH, which is supraphysiologic as compared with the more physiologic low-dose (0.5 µg) test.⁸

In summary, we have shown that 200 µg once daily intranasal FP produced statistically significant suppression (43%) in terms of the effects on overnight urinary cortisol excretion, whereas suppression with TAA (23%) and BDP (21%) was not statistically significant. Because both rhinitis and asthma are atopic conditions and frequently coexist, it is important to consider the total systemic burden caused by both inhaled and intranasal corticosteroid therapy.

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