

Effect of intranasal fluticasone propionate and triamcinolone acetonide on basal and dynamic measures of hypothalamic–pituitary–adrenal-axis activity in healthy volunteers

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Summary

Background Most published studies show that intranasal corticosteroids have no effect on the hypothalamic–pituitary–adrenal (HPA) axis, but there have been isolated reports to the contrary, contradicting accumulated knowledge on pharmacokinetics.

Objective To re-evaluate the effect of fluticasone propionate aqueous nasal spray (FPANS) and triamcinolone acetonide (TAA) aqueous nasal spray on the HPA axis using an improved study design.

Methods Twenty-three healthy volunteers were randomized in a double-blind, three-way crossover study. The study comprised a 4-day placebo run-in phase followed by three 4-day treatment periods (placebo, FPANS (200 µg once daily) or TAA aqueous nasal spray (220 µg once daily)), separated by 7–14 days washout intervals. Before the first, and on the last day of each treatment period, 12-h overnight urine was collected to assess cortisol excretion and cortisol creatinine ratio. Approximately 26 h after the last administration of study medication, volunteers underwent stimulation with 0.5 µg adrenocorticotrophic hormone (ACTH). Serum cortisol concentrations were measured before and 20 and 30 min after injection. Blood and urine samples were analysed for cortisol by liquid chromatography tandem mass spectrometry.

Results Compared with placebo, FP or TAA had no significant effect on mean overnight (12 h) urinary cortisol excretion, and did not significantly suppress the overnight geometric mean urinary cortisol/creatinine excretion ratio. Values for serum cortisol before and after ACTH stimulation showed no significant suppression, although there was a slight blunting of the HPA-axis response following TAA treatment.

Conclusion This study confirms that there are no detectable effects on the HPA axis following short-term intranasal FP or TAA at their recommended dosages.

Keywords cortisol, fluticasone propionate, hypothalamic–pituitary–adrenal axis, intranasal corticosteroids, triamcinolone acetonide

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Introduction

Allergic rhinitis is the most common of all atopic diseases [1, 2], affecting up to 20% of the adult population [3]. It is responsible for high morbidity and more absences from work/school than any other chronic disease [4], and has a major impact on the quality of life of the sufferer [5]. Intranasal corticosteroids are a first-line therapy for the treatment of rhinitis, and their efficacy and safety for the management of this condition are well established [6–9].

The weight of clinical and pharmacokinetic evidence in the published literature shows that treatment with fluticasone propionate (FP) aqueous nasal spray (FPANS) is unlikely to cause clinically relevant hypothalamic–pituitary–adrenal

(HPA)-axis suppression [9–12]. However, some studies in healthy volunteers and patients with rhinitis have produced conflicting results [13–15]. A study by Wilson et al. [13] in healthy volunteers showed that intranasally administered triamcinolone acetonide (TAA; 220 µg once daily), beclomethasone dipropionate (BDP; 336 µg once daily) or FP (200 µg once daily) reduced overnight (9.5 h) urinary-free cortisol excretion in a group of 16 healthy volunteers, although this decrease was statistically significant for intranasal FP only. When creatinine-corrected overnight (9.5 h) urinary cortisol was assessed, the effects of FPANS did not significantly differ from those of placebo [13]. The values for serum cortisol before and after adrenocorticotrophic hormone (ACTH) stimulation also showed no significant suppression and, in agreement with other results, treatment with FPANS, TAA and BDP was not associated with a blunting of the response to low-dose (0.5 µg) ACTH stimulation [13, 16].

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The Wilson et al. [13] study produced results that were contradictory to what is known about the pharmacokinetics of FP, which may have been due to study design limitations. For example, urine samples were collected over a 9.5-h period, from 22:00 to 07:30 hours, rather than the standard 12-h period [17, 18]. In addition, a radioimmunoassay method was used to assay cortisol, which is prone to cross-reactivity/interference especially from closely related structures such as metabolites of cortisol. Therefore, we decided to compare directly the systemic activity of FPANS (200 µg once daily), TAA (220 µg once daily) and matching placebos in healthy human volunteers using an improved and more robust double-blind double-dummy study design to that previously used [13], and the more specific method of liquid chromatography tandem mass spectrometry (LC-MS/MS) to assay cortisol concentrations in urine and serum. Urine collections were for 12-h periods to 09:30 hours the following morning, during which time the cortisol excretion is near optimal in relation to the overnight secretory activity.

Materials and Methods

Study population

Healthy non-atopic males or females (18–65 years inclusive) were eligible for entry into the study. All volunteers had normal parameters of routine blood and urine analysis. To avoid the risk of anaphylactic reactions after administration of ACTH, volunteers were excluded if they had a positive skin prick test (>3 mm) to inhalant allergens such as house dust mite, grass or tree pollen allergens. Volunteers were also excluded if they had: serious or unstable concurrent disease; concurrent purulent nasal infection; previous treatment with systemic, intranasal or inhaled corticosteroids or sodium cromoglycate for a recommended 3 months before the study; a history or suspicion of alcohol, barbiturate, amphetamine or narcotic abuse; or were being treated with any regular medication except contraception (in the case of females). All volunteers signed an informed consent form before enrolment in the study.

Randomization and blinding

The random code was generated using a validated in-house system, Patient Allocation for Clinical Trials. The participating centre for the study was supplied with a list of subject numbers, which were assigned to volunteers in ascending order, starting with the lowest treatment number available. Study drugs were labelled to ensure that both patient and investigator were blinded to treatment allocation.

Study design

The study had a double-blind, randomized, single-centre, three-way crossover placebo-controlled design. The study protocol was approved by the Investigational Centre Ethics Committee, and the study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. Volunteers received the following three intranasal treatments in random order:

- FPANS (200 µg once daily) plus placebo to match TAA once daily, or
- TAA (220 µg once daily) plus placebo to match FPANS once daily, or
- placebo to match FPANS once daily plus placebo to match TAA once daily.

Volunteers administered each treatment once daily, two squirts up each nostril at 08:00 hours for 4 days. Before randomization volunteers completed a 4-day placebo run-in period, taking both placebo sprays according to the same schedule. Treatment periods were separated by 7–14-day washout intervals. There was 1 day between the run-in phase and the first treatment period.

Measurements

The day after the run-in phase and the day after each treatment period, volunteers underwent ACTH stimulation. Between 09:30 and 10:00 hours (i.e. approximately 26 h after taking the last dose of medication), volunteers were given 0.5 µg ACTH intravenously. Thirty minutes before stimulation, a cannula was inserted into the volunteers' antecubital fossa vein. For later measurements of serum cortisol, blood samples (7.5 mL) were taken immediately before and at 20 and 30-min post-stimulation. From the beginning to the end of these procedures, volunteers rested in the supine position.

During the night after the last day of each treatment period, and during the night preceding the last day before each treatment period, volunteers performed a 12-h urine collection starting between 21:00 and 21:30 hours for the assessment of urinary cortisol concentrations. After recording the volume, the specimen aliquots were kept for cortisol and creatinine assay.

Assay

Cortisol concentrations in both urine and serum were assayed by LC-MS/MS, using a Perkin-Elmer Sciex API III Plus biomolecular mass analyzer (PE SCIEX, Ontario, Canada). Cortisol was extracted from plasma and urine samples using ethyl acetate under alkaline conditions. The liquid chromatography conditions were as follows: injection volume, 20 µL; mobile phase, methanol/water/concentrated formic acid (80/20/0.05); flow rate, 0.55 mL/min (flow split at 20:1); analytical column, Luna C18 5 µm 250 mm × 4.6 mm (Phenomenex, Torrance, CA, USA). This assay has been validated to measure plasma cortisol concentrations in the range 0.51–250.15 ng/mL and urinary cortisol concentrations in the range 0.50–251.70 ng/mL.

Adverse events

An adverse event was defined as any untoward medical occurrence experienced by a volunteer that does not necessarily have a causal relationship with the treatment received. All adverse events were documented and rated as mild, moderate or severe.

Statistical analysis

The primary end-point of the study was serum cortisol concentrations pre- and post-ACTH stimulation, measured at

the end of each treatment period. The peak response to ACTH stimulation was considered to be the higher of the samples taken after 20 or 30 min. Serum cortisol concentrations for each treatment were compared using an analysis of variance adjusting for effects due to baseline, subject and period. Pairwise comparisons were also constructed and adjusted using the Tukey–Kramer method. Secondary endpoints included overnight urinary cortisol concentrations and the ratio of urinary cortisol to creatinine at the end of each treatment period, and were analysed using an analysis of variance allowing for effects due to baseline, subject and period, and pairwise comparisons made using contrasts which were then adjusted using the Tukey–Kramer method. The urinary cortisol/creatinine ratio baseline was taken as the ratio recorded before the start of each treatment period. All tests were performed at an overall significance level of 5%, and adjusted 95% confidence intervals were calculated for all estimates of treatment difference. Values are given in the text as means $\pm$ standard error.

Results

Twenty-five volunteers were enrolled into the study and 23 were randomized to treatment and included in the intent-to-treat analysis. Volunteer baseline characteristics are shown in Table 1.

Overnight urinary cortisol excretion

Neither FPANS ($P = 0.609$) nor TAA ($P = 0.194$) significantly suppressed basal measures of HPA-axis activity compared with placebo, as assessed by mean overnight urinary cortisol excretion (Fig. 1). In the FPANS group, the overnight urinary cortisol concentration was 29.6 ± 4.2 nmol pre-treatment and 32.5 ± 4.3 nmol post-treatment compared with 29.8 ± 4.8 nmol/ 39.1 ± 5.3 in the TAA group and 30.7 ± 3.5 nmol/ 28.5 ± 3.3 in the placebo group. When one outlier value was excluded from the end of FPANS treatment, the finding was the same and FPANS did not significantly suppress the mean overnight urinary cortisol concentration (30.2 ± 3.8 nmol) compared with placebo ($P = 0.753$).

FPANS ($P = 0.374$) or TAA ($P = 0.107$) also did not significantly affect overnight urinary cortisol/creatinine excretion compared with placebo (FPANS 5.3 nmol/nmol; TAA 6.0 nmol/nmol; placebo 4.3 nmol/nmol). After removal of the outlier value from the end of FPANS treatment, the overnight urinary cortisol/creatinine ratio in the FPANS group was 4.8 nmol/nmol, which did not significantly ($P = 0.757$) differ from placebo.

Serum cortisol concentrations

FPANS ($P = 0.999$) or TAA ($P = 0.521$) had no significant effect on dynamic measures of HPA-axis activity compared with placebo as assessed by mean peak serum cortisol concentrations before and after ACTH stimulation (Table 2). The mean peak serum cortisol concentration post-ACTH stimulation was observed at 30 min for each treatment. However, there was a slight blunting of the HPA-axis response following TAA treatment. In the TAA group there

was a 28.2% increase in serum cortisol concentration following ACTH stimulation compared with 59.5% in the FPANS group and 52.2% in the placebo group. Mean serum cortisol concentrations 20 and 30 min after ACTH stimulation are shown in Table 2.

Adverse events

Both treatments were well tolerated, and there was no significant difference in the number of volunteers who

Table 1. Volunteer baseline characteristics

Age (years) $\pm$ SD	41.8 $\pm$ 13.0
Sex, number (%)	
Male	16 (70%)
Female	7 (30%)
Height (cm) $\pm$ SD	175.0 $\pm$ 8.6
Weight (kg) $\pm$ SD	76.8 $\pm$ 15.1
Serum cortisol concentration (nmol/L) $\pm$ SE	
Pre-ACTH	333.10 $\pm$ 38.26
20-min post-ACTH	516.82 $\pm$ 42.17
30-min post-ACTH	510.45 $\pm$ 46.86
12-h urinary cortisol concentration (nmol) $\pm$ SE	
Pre-FPANS period	29.55 $\pm$ 4.20
Pre-TAA period	29.82 $\pm$ 4.80
Pre-placebo period	30.68 $\pm$ 3.45

SD, standard deviation; SE, standard error; ACTH, adrenocorticotrophic hormone (0.5 μ g); FPANS, fluticasone propionate aqueous nasal spray; TAA, triamcinolone acetonide.

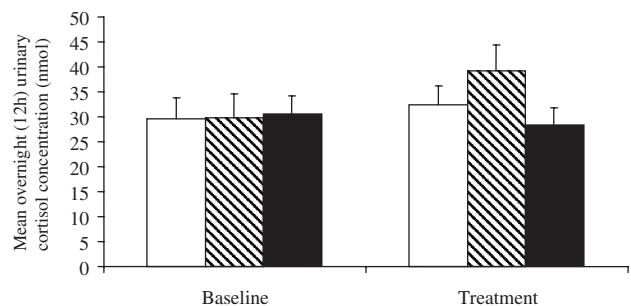


Fig. 1. Effect of intranasally administered fluticasone propionate (200 μ g once daily), triamcinolone acetonide (220 μ g once daily) or placebo on mean overnight (12 h) urinary cortisol concentrations in healthy volunteers. $\square$ fluticasone propionate aqueous nasal spray (200 μ g od); $\square$ triamcinolone acetonide aqueous nasal spray (220 μ g od); $\blacksquare$ placebo. Results are expressed as mean $\pm$ standard error.

Table 2. Effect of intranasal FP, TAA and placebo on serum cortisol concentrations before and after ACTH stimulation

Treatment	Pre-ACTH (nmol/L)	20-min post-ACTH (nmol/L)	30-min post-ACTH (nmol/L)
Placebo	320.1 $\pm$ 50.7	468.8 $\pm$ 44.8	487.3 $\pm$ 64.7
FPANS (200 μ g od)	357.9 $\pm$ 52.6	561.2 $\pm$ 71.9	570.7 $\pm$ 72.6
TAA (220 μ g od)	372.3 $\pm$ 78.0	457.2 $\pm$ 37.8	477.1 $\pm$ 43.1

Results are expressed as the mean $\pm$ standard error. FPANS, fluticasone propionate aqueous nasal spray; TAA, triamcinolone acetonide aqueous nasal spray; ACTH, adrenocorticotrophic hormone.

experienced an adverse event during treatment ($n = 1$ receiving FPANS; $n = 2$ receiving TAA group; $n = 3$ receiving placebo). The most common adverse event was the occurrence of a respiratory tract infection ($n = 1$ TAA; $n = 1$ placebo). None of the adverse events reported were considered to be drug related, and no serious adverse events were reported during the study.

Discussion

The results of our study confirm that at clinically recommended doses, short-term administration of FPANS or TAA produced no detectable effects on the HPA axis. FPANS or TAA had no significant effect on early morning serum cortisol concentrations basally and after ACTH stimulation, 12-h overnight urinary cortisol excretion or overnight urinary cortisol/creatinine ratios.

The weight of clinical and pharmacokinetic evidence in the published literature supports our results, and shows that, as predicted from its low systemic bioavailability, treatment with intranasal FP is unlikely to cause clinically relevant HPA-axis suppression. The results of larger studies in volunteers [8] and patients [10, 11], lasting between 7 days and 4 weeks, show that substantially higher doses of intranasal FP have no significant effects on 24-h urinary-free cortisol concentrations. In addition, numerous studies ranging in duration from 2 weeks to 1 year have shown that intranasal FP has no significant effect on mean morning plasma cortisol concentrations [9, 12, 19–22] or ACTH stimulation tests [9, 20, 22] compared with placebo.

Some studies, however, have reported significant effects of intranasal corticosteroids on serum osteocalcin [14], blood eosinophil counts [15] and cortisol excretion in urine collected from 22:00 to 07:30 hours [13], but several limitations in those studies make them less than ideal for assessing effects of intranasal corticosteroids on the HPA axis. For example, Wilson et al. [13] showed that FPANS significantly reduced overnight (9.5 h) urinary cortisol concentrations (43% suppression), but the reduction attributed to FPANS was not statistically significant by the more appropriate assessment of creatinine-corrected overnight urinary cortisol [23]. Values for serum cortisol before and after ACTH stimulation also showed no significant suppression [13]. The duration and timing of urine collection will influence the interpretation of findings. Cortisol is normally mainly secreted during the night, in a series of peaks with intervals of approximately 90 min. The last peak in cortisol secretion varies in individuals between 06:00 and 10:00 hours. Inhaled corticosteroids can delay the onset of this pulsatile pattern resulting in fewer peaks, but rarely obliterates the pattern, so that blood cortisol concentrations at approximately 08:00 hours are within the normal range. However, urinary cortisol excretion is delayed by 2–4 h after the plasma changes, so overnight urine collected up to 07:30 hours will have a lower proportion of the total secreted cortisol than urine collected up to 09:30 hours or later. Comparison of the data in the present study (12-h collection period) with that of Wilson et al. [13] (9.5-h collection period) confirms this statement. A 12-h urine collection to 09:30 hours for cortisol measurements carried

out in the present study is thus a better indicator of adrenal function. McIntyre et al. [23] have already made that proposal, although the collection periods were not defined. For a true assessment of changes in the HPA axis, blood samples need to be collected overnight at frequent intervals [24], which, although more accurate, is technically difficult and the physiological effects of being woken frequently during the night may contribute to the variation observed.

By examining the large amount of data available on the systemic effects of inhaled corticosteroids, it is possible to calculate the approximate plasma concentrations of FP that would be needed to cause a fall of approximately 50% in plasma cortisol concentrations, and to extrapolate this to urinary cortisol concentrations. The approximate 24-h area under the curve of FP needed to achieve a mean fall of 50% in plasma cortisol concentrations is 3200 pg h/mL. The highest blood concentration of FP that has been reported after intranasal dosing is 68 pg h/mL [25], and so to detect the approximate 40% reduction in urinary cortisol concentrations following intranasal dosing of FP, observed in the study by Wilson et al. [13], approximately 200 times the therapeutic dose of FP would have to be given in a single dose.

An earlier study carried out by Knutsson et al. [14] investigated the effect of intranasal corticosteroids on serum cortisol, osteocalcin and urinary cortisol concentrations, but did not contain a placebo group. The changes in serum osteocalcin observed were consistent with changes over time and *not* with a systemic effect of intranasal corticosteroids. This was confirmed by the fact that serum cortisol concentrations remained within the normal range, and a normal serum cortisol response occurred upon stimulation with ACTH, indicating maintenance of HPA-axis integrity [14]. Interestingly, a more recent study from the same group involved dosing patients at concentrations of up to 800 µg of nasal budesonide, and on this occasion no significant effects on morning serum cortisol were observed [26], confirming our view of the original study. Although oral corticosteroids are well known to have effects on bone density [27], there is now accumulating evidence that intranasal and inhaled corticosteroids at recommended dosages appear to have little effect on bone density and metabolism, as measured by markers of bone resorption and formation, and by techniques used to measure cortical and trabecular bone density [28].

In the study by Foresi et al. [15], the effect attributable to FP (i.e. reduction in eosinophil numbers) was consistent with a topical anti-inflammatory effect of a corticosteroid, subsequently diminishing the signal to the bone marrow [29], which indirectly reduced the number of circulating eosinophils. Foresi et al. [15] also failed to show a significant suppression by intranasal FP on 24-h urinary cortisol excretion.

In our study, the fact that FPANS did not significantly suppress 12-h overnight urinary cortisol or ACTH-stimulated serum cortisol concentrations is not surprising, since FP has negligible oral and intranasal bioavailability [25, 30]. Bioavailability is the main predictor for the potential of corticosteroids to cause systemic effects. As the major portion of intranasal corticosteroids is swallowed, their oral bioavailabilities are important when determining their potential to cause systemic effects. The oral bioavailability of FP is negligible (<1%) [30] compared with that of TAA (23%) [31]. FP also has a negligible nasal bioavailability (0.5%) [25],

substantially lower than that of other intranasal corticosteroids (TAA = 44%, BDP = 44%, BUD = 31%) [32], which relates to its extremely low water solubility. Thus, clinically significant systemic effects following treatment with the recommended daily dose of FPANS are highly unlikely in patients. The low oral bioavailability of FP is due to its poor absorption and extensive first-pass metabolism to an inactive derivative [8, 33]. The dissolution rate of FP is also slow, and so the contact time with the mucosa probably limits the opportunity for rapid absorption across the mucosa of the nose.

The results of our study confirm that there are no detectable effects on the HPA axis following intranasal dosing with FP or TAA at recommended dosages. Experimental design is critical to obtaining meaningful data in these complex studies. Variables that can affect cortisol concentration measurements and lead to misleading results include timing of sample collections, nature of the samples, assay performance as well as the differing uptake, distribution and metabolism of the drugs being studied.

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