

Dose-response comparison of systemic bioactivity with inhaled budesonide and triamcinolone acetonide in asthmatic adults

Andrew M. Wilson, MBChB, MRCP, Helen J. A. Brewster, RGN, and Brian J. Lipworth, MD, FRCP Dundee, Scotland

Background: Budesonide (BUD) has recently been licensed for treatment of asthma in the United States, whereas triamcinolone acetonide (TAA) has been used for many years.

Objective: We sought to evaluate the dose-response effect of inhaled BUD and TAA in terms of adrenal, bone, and blood markers.

Methods: Twelve asthmatic subjects (mean age, 32 years; mean FEV₁, 91% of predicted value) were studied in a randomized design comparing 3 days of treatment with placebo and low (200 µg twice daily), medium (400 µg twice daily), and high (800 µg twice daily) doses of BUD (Pulmicort Turbuhaler, 100 µg) and TAA (Azmecort integrated actuator/spacer, 100 µg) with a 7-day period at crossover, when patients received their usual inhaled corticosteroid therapy. Measurements were made at 8 AM for serum cortisol, osteocalcin, and blood eosinophils. Measurements were also made for overnight urinary cortisol/creatinine excretion.

Results: For all measurements there were no significant differences between the 2 treatments at any dose level. Ratios between BUD and TAA (95% CI) at the highest dose levels were as follows: 8 AM serum cortisol, 1.08-fold (0.63 to 1.85); urinary cortisol, 1.09-fold (0.63 to 1.86); eosinophils, 0.98-fold (0.69 to 1.38); and osteocalcin 1.05-fold (0.78 to 1.41). There was no evidence of a significant overall dose-response effect for any parameter of hypothalamo-pituitary-adrenocortical axis activity, with neither drug being significantly different from placebo at any dose. For the 3 dose levels of both drugs, total abnormal low values for 8 AM serum cortisol (ie, <5.4 µg/dL [<150 nmol/L]) showed 2 of 36 for BUD and 2 of 36 for TAA. There was also no significant overall dose-response effect for eosinophils or osteocalcin, although both drugs were significantly ($P < .05$) different from placebo at the highest dose: eosinophils ($\times 10^9/L$), placebo: 0.36, TAA: 0.24, and BUD: 0.23; and osteocalcin (nmol/L), placebo: 1.04, TAA: 0.73, and BUD: 0.77.

Conclusion: There were no significant differences in the systemic bioactivity profiles, in terms of adrenal, blood, and bone markers, between BUD administered by means of Turbuhaler and TAA administered by means of an integrated actuator/spacer in a dose range of 400 µg to 1600 µg/day. Both

drugs exhibited a significant degree of detectable systemic bioactivity but only at the highest dose of 1600 µg/day for effects on eosinophil count and osteocalcin. (*J Allergy Clin Immunol* 1998;102:751-6.)

Key words: Adrenal suppression, asthma, corticosteroids, budesonide, triamcinolone acetonide, bone markers, eosinophils

Inhaled corticosteroids are regarded throughout Europe and the United States to be the first line antiinflammatory therapy for the treatment of asthma. Indeed, current national and international management guidelines suggest that inhaled corticosteroids should be prescribed in all but the most mild cases of asthma and especially for those subjects who require regular reliever therapy with β_2 agonists.^{1,2} It is now widely accepted that all inhaled corticosteroids are associated with similar dose-related systemic adverse effects as occur with oral corticosteroids, although they do have a better therapeutic index.³

The most important long-term systemic adverse effect of corticosteroids is that of osteoporosis and the increased risk of fracture,⁴ mainly in the more metabolically active trabecular bones such as the vertebrae. Among other mechanisms, glucocorticoids cause osteoporosis by decreasing the function of osteoblasts, thereby altering the balance of bone formation and resorption. Osteocalcin, a protein secreted by osteoblasts, can be used as a marker of systemic activity by measuring changes in serum concentration.

Adrenal suppression is a sensitive and reproducible marker of the systemic bioavailability of inhaled corticosteroids.⁵ Overnight urinary cortisol excretion, especially when corrected for creatinine excretion, is recognized to be as sensitive as the more cumbersome 24-hour urinary cortisol excretion and more sensitive than 8 AM serum cortisol.⁶ Suppression of blood eosinophil count is also a sensitive measure of the systemic effects of steroids⁵ and can be regarded as a marker of the total systemic allergic burden.

Triamcinolone acetonide (TAA) administered by means of an integrated actuator/spacer is a commonly used inhaled corticosteroid in the United States, whereas budesonide administered by means of the Turbuhaler has recently become licensed for use in the US. Therefore it was believed to be important to perform a dose-response study in asthmatic patients to assess the relative effects

From the Department of Clinical Pharmacology and Therapeutics, Ninewells Hospital & Medical School, University of Dundee, Dundee.

Supported by Rhone-Poulenc Rorer, Inc.

Received for publication Dec 15, 1997; revised June 30, 1998; accepted for publication June 30, 1998.

Reprint requests: Brian J. Lipworth, Department of Clinical Pharmacology and Therapeutics, Ninewells Hospital & Medical School, University of Dundee, Dundee DD1 9SY, Scotland, UK.

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0091-6749/98 \$5.00 + 0 1/1/93065

Abbreviations used

BUD:	Budesonide
CV:	Coefficient of variation
FEF ₂₅₋₇₅ :	Forced expiratory flow between 25% and 75% of forced vital capacity
HPA:	Hypothalamo-pituitary-adrenocortical
TAA:	Triamcinolone acetate

for these 2 drugs on systemic bioactivity markers. The doses chosen represent the low, medium, and highest recommended licensed dose of both drugs. Also, the medications were compared on a microgram equivalent basis because this is how they are likely to be prescribed in everyday clinical practice.

METHODS

Patients

Twelve patients with stable, mild-to-moderate asthma⁷ were recruited into the study. Their mean age (SEM) was 32.0 years (3.6 years), mean FEV₁ was 91.0% (4.16%) of predicted value, and mean forced expiratory flow between 25% and 75% of forced vital capacity (FEF₂₅₋₇₅) was 65.8% (6.7%) of predicted value. All patients were receiving less than or equal to 1200 µg/day of inhaled corticosteroid (median dose: 500 µg/day, range: 100 to 1200 µg/day; beclomethasone dipropionate: *n* = 7, BUD: *n* = 3, and fluticasone propionate: *n* = 2). No patient had received oral corticosteroids within the previous 6 months. All subjects had normal full blood counts and biochemical profiles (including urea and electrolytes, liver function tests, and bone markers) and normal urinalysis. Approval for the study was obtained from the Tay-side Medical Ethics Committee, and all subjects gave written informed consent.

Study design

A single (investigator) blind, placebo-controlled, randomized crossover design was used. Subjects attended an initial screening where FEV₁ and FEF₂₅₋₇₅ were measured with a Vitalograph Compact spirometer (Vitalograph Ltd, Buckingham, UK). They were eligible for inclusion in the study if their FEV₁ was greater than 70% of predicted value. Spirometry was also measured at each subsequent visit, although efficacy was not an end point due to the short duration of treatment. Patients were randomized to receive either inhaled BUD 100 µg per inhalation (administered by Pulmicort Turbuhaler, Astra Pharmaceuticals Ltd) or inhaled TAA 100 µg per actuation (as Azmacort with integrated actuator/spacer, Rhone-Poulenc Rorer Inc).

Each drug sequence was given over a total of 9 days, with 6 patients receiving BUD first in sequence and the other 6 patients receiving TAA first in sequence. Both treatments were given in twice daily divided doses at 8 AM and 10 PM. The doses for both BUD and TAA were given sequentially for 3 days as 2 puffs twice daily, 4 puffs twice daily, and 8 puffs twice daily (400 µg/day, 800 µg/day, and 1600 µg/day, respectively). Before each 9-day drug sequence (either BUD or TAA), patients received 2 puffs twice daily from the corresponding placebo inhaler (Turbuhaler or integrated spacer) for 3 days. The patients' usual inhaled corticosteroid therapy was discontinued during the placebo and treatment periods. There was also a 7-day washout period between each of the 9-day treatment sequences during which patients received their usual maintenance inhaled corticosteroid therapy. Each

inhaler was discharged twice before use, and each inhalation was followed by mouth rinsing.

All the inhalers were masked and sealed in envelopes by a pharmacist along with instruction sheets at the beginning of the trial to make it investigator blind. Before the study and at each visit, subjects were given detailed instructions by a third party in how to use their inhalers. The patients used the appropriate training device: Turbuhaler usage trainer (Astra Draco, Lund, Sweden) or Vitalograph aerosol inhalation monitor device (Vitalograph, Bucks, UK). The patients were not permitted to proceed into the study unless they had near perfect technique by "passing" the trainer/monitor device test. This included correct inspiratory flow rate and, in the case of the pressurized metered-dose inhaler, correct timing of actuation. Each subject received a written instruction sheet that was based on the manufacturer's recommended device operation and inhalation technique to follow while using their inhaler at home, and a simple tick chart was used as an aide to compliance. Data from patients with more than 90% compliance were considered to be evaluable.

Measurements

The subjects attended the laboratory at 7:30 AM, 9½ hours after taking the sixth dose (at 10 PM) of inhaled medication or placebo. A cannula was inserted into the antecubital fossa vein to permit blood sampling, and subjects then rested supine for 30 minutes. After the rest period, blood samples were taken for measurement of serum cortisol, serum osteocalcin, and blood eosinophils at 8 AM. Patients were asked to empty their bladder at 10 PM on the third day of placebo or active treatment and collect all voided urine from 10 PM until arriving at the department. They completed the collection after voiding another sample after the blood sample at 8 AM. The volume of the total sample was recorded, and aliquots were taken for urinary cortisol and creatinine.

Assays

All assays were performed in duplicate in a blinded fashion by a separate technician. Serum cortisol was measured with a commercial RIA kit (Incstar Ltd, Wokingham, Berkshire, UK), which has no cross reactivity for either steroid. The coefficient of variation (CV) for analytic imprecision for serum cortisol was 5.5% within the assay and 10.9% between the assay. For urinary free cortisol excretion, the within-assay CV was 7.9% and the between-assay CV was 12.1%. Urinary creatinine was measured on a Cobas-bio autoanalyzer (Roche Products Ltd, Welwyn Garden City, Herts, UK). The intraassay CV was 1.92%, and the interassay CV was 4.9%. Serum osteocalcin was measured with an RIA kit (Incstar Ltd). The within-assay CV was 5.9%. The eosinophil count was measured with an SE-9000 Haematology analyzer (Sysmex UK Ltd, Bucks, UK). The lower limit of the normal reference range for 8 AM serum cortisol in our laboratory is 5.4 µg/dL (150 nmol/L), and that for overnight urinary cortisol excretion is 3.6 µg (10 nmol).

Statistical analysis

The study was designed with a sample size of 12 with 80% power (β error = .2) to detect 20% cortisol suppression, and the α error was set at .05 (2-tailed). All data were analyzed with a Statgraphics software package (STSC Software Group, Rockville, Md). All data apart from 8 AM serum cortisol were analyzed geometrically to normalize their distributions.

All active treatments and both placebos were compared by an overall multifactorial analysis of variance by using treatment, dose, subject, and period as factors followed by Bonferroni's multiple range testing to obviate multiple pair-wise comparisons. The Bonferroni's multiple range test was set with 95% confidence intervals, and hence any significant differences are reported at the *P* < .05 level. At the highest dose level, the response ratio and 95% confi-

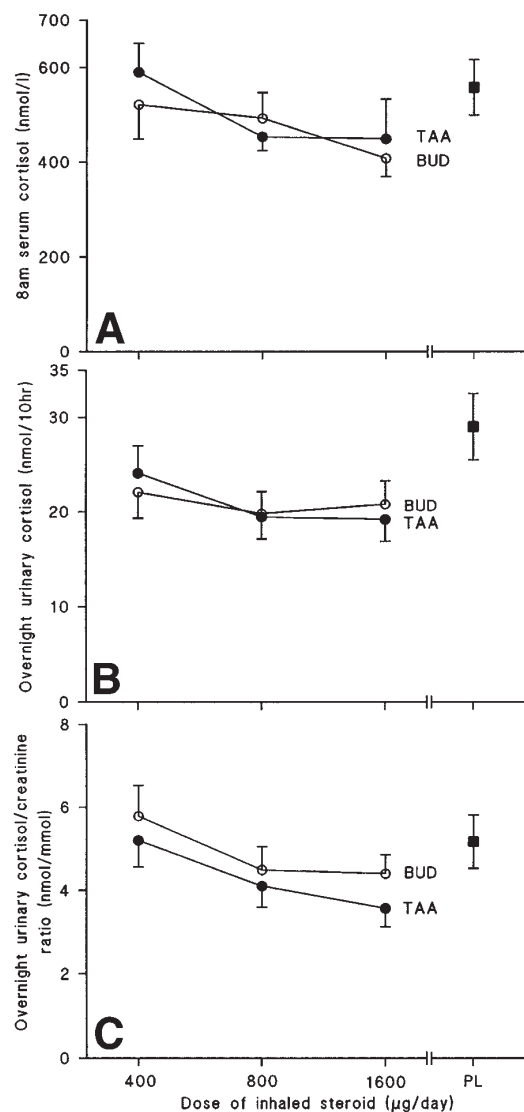


FIG 1. Geometric means (SE) for BUD and TAA 400 µg/day, 800 µg/day, and 1600 µg/day for 8 AM serum cortisol (**A**), overnight urinary cortisol excretion (**B**), and overnight corrected cortisol/creatinine ratio (**C**). There was no overall dose-related suppression or significant difference between pooled placebo (PL) and either corticosteroid for any marker or HPA-axis activity.

dence interval between the 2 drugs (BUD:TAA) were also calculated. Ratios including unity indicate a nonsignificant ($P < .05$) difference. The presence of dose-related suppression was evaluated by using least-squares regression analysis to evaluate the overall effects of all 3 dose levels for each drug. The number of individual values of 8 AM serum cortisol or overnight urinary cortisol with an abnormal level less than 5.4 µg/dL (150 nmol/L) or 3.6 µg/10 hours (10 nmol/10 hours), respectively, were analyzed by using the chi-square test.

RESULTS

There were no significant carryover effects between the first and second placebos in sequence by using any of

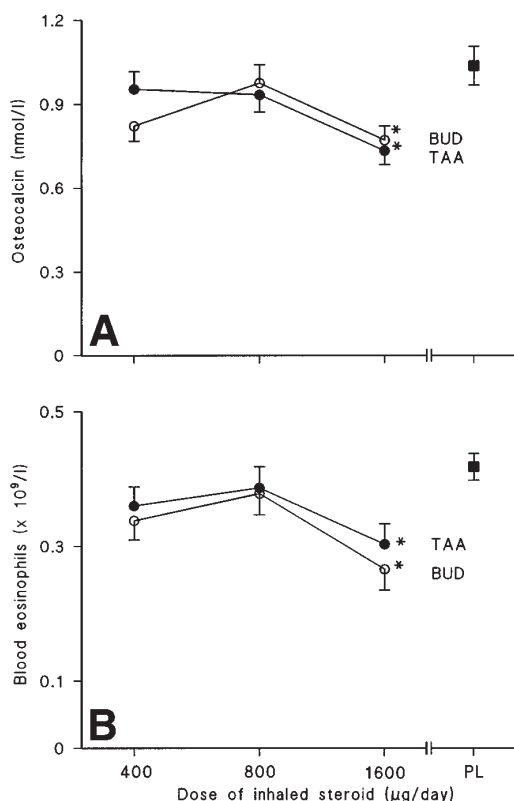


FIG 2. Geometric means (SEM) for BUD and TAA 400 µg/day, 800 µg/day, and 1600 µg/day for serum osteocalcin (**A**) and blood eosinophil count (**B**). There was no overall dose-related suppression for either marker. Asterix denotes significant ($P < .05$) difference between either corticosteroid and pooled placebo (PL).

the systemic parameters measured (Table I). There were no significant differences between the FEV₁ values (as percent predicted) comparing pooled placebo with low, medium, or high doses of each drug: placebo, 84.3%; low-dose BUD, 83.7%; medium-dose BUD, 85.4%; high-dose BUD, 84.8%; low-dose TAA, 83.6%; medium-dose TAA, 88.3%; and high-dose TAA, 85.4%. FEF₂₅₋₇₅ values (as percent predicted) were as follows: placebo, 57.5%; BUD, 58.8%; medium-dose BUD, 58.7%; high-dose BUD, 60.8%; low-dose TAA, 57.5%; medium-dose TAA, 63.3%; high-dose TAA, 56.7%.

Hypothalamo-pituitary-adrenocortical axis

There were no significant differences in any of the markers of hypothalamo-pituitary-adrenocortical (HPA)-axis activity between the 2 drugs. Ratios and 95% confidence intervals for difference (BUD:TAA) at the high dose (1600 µg/day) were as follows: serum cortisol, 1.08 (0.63 to 1.85); overnight urinary cortisol, 1.09 (0.63 to 1.86); and overnight urinary cortisol/creatinine, 1.24 (0.71 to 2.15). There was also no significant dose-related suppression from overall analysis of the 3 doses for each drug. There was also no significant difference between pooled placebo and any of the dose levels of either drug (Fig 1). When

TABLE I. Geometric means (SEM) for the first placebo in sequence, the second placebo in sequence, the placebo given before TAA, and the placebo given before BUD for 8 AM serum cortisol, overnight urinary cortisol excretion, overnight corrected cortisol/creatinine, osteocalcin, and eosinophils

	First PL	Second PL	TAA-PL	BUD-PL
8 AM serum cortisol (nmol/L)	566.60 (75.2)	548.69 (47.0)	594.20 (72.5)	521.09 (48.8)
Overnight urinary cortisol (nmol/10 h)	25.61 (3.23)	29.18 (3.68)	22.60 (2.78)	33.05 (4.06)
Overnight urinary cortisol/creatinine (nmol/mmol)	4.46 (0.55)	5.55 (0.69)	4.39 (0.54)	5.64 (0.69)
Osteocalcin (nmol/L)	1.03 (0.07)	1.01 (0.07)	1.01 (0.07)	1.03 (0.07)
Eosinophils ($\times 10^9/L$)	0.39 (0.03)	0.33 (0.03)	0.39 (0.03)	0.33 (0.03)

There was no significant difference between any of the placebos.

First PL, First placebo in sequence; Second PL, second placebo in sequence; TAA-PL, placebo given before TAA; BUD-PL, placebo given before BUD.

comparing all doses of both drugs, there was no significant difference in the total number of individual results with abnormal low values for 8 AM cortisol less than 5.4 $\mu\text{g/dL}$ (150 nmol/L) (TAA [$n = 2$ of 36] vs BUD [$n = 2$ of 36]) or for overnight urinary cortisol less than 3.6 $\mu\text{g}/10$ hours (10 nmol/10 hours) (TAA [$n = 4$] vs BUD [$n = 3$]).

Osteocalcin and eosinophils

There were no significant differences in either serum osteocalcin or blood eosinophils between the 2 treatments. Ratios (BUD:TAA) and 95% confidence intervals for difference at the high (1600 μg) dose were as follows: eosinophils, 0.98 (0.69 to 1.38); and osteocalcin, 1.05 (0.78 to 1.41). There was no significant overall dose-related suppression. There was a significant ($P < .05$) difference between pooled placebo and both of these markers at the high dose only (Fig 2): eosinophils ($\times 10^9/L$), placebo: 0.36, high-dose TAA: 0.24, and high-dose BUD: 0.23; and osteocalcin (nmol/L), placebo: 1.04, high-dose TAA: 0.73, and high-dose BUD: 0.77.

DISCUSSION

We found no significant differences between inhaled BUD and TAA administered at a dose range of 400 $\mu\text{g/day}$ to 1600 $\mu\text{g/day}$ in patients with mild-to-moderate asthma for all of the measured markers of systemic activity. Indeed, only blood eosinophils and serum osteocalcin showed any significant suppression compared with placebo, and this occurred only at the highest dose level of 1600 $\mu\text{g/day}$. To explain these findings, it is pertinent to consider the relative pharmacologic properties of both drugs. BUD has greater topical potency than TAA, as measured by the MacKenzie skin vasoconstrictor assay,⁸ but a similar receptor residency half-time (BUD, 5.7 hours vs TAA, 3.9 hours).^{9,10} The effect of corticosteroids are not the same on different tissue markers.^{11,12} Although the MacKenzie skin vasoconstrictor assay is a convenient measure of potency, it does have its limitations because the topical effect on the skin does not necessarily mirror systemic activity in adrenal, bone, or blood tissues. It is therefore unclear whether any difference in topical potency will translate into commensurate differences in systemic bioactivity.

When considering antiasthmatic efficacy and systemic effects of inhaled corticosteroids, we must take into account both the potency of the drug and the lung dose to the patient. In this respect it has been shown that the respirable fraction of TAA as Azmacort administered by means of the integrated spacer/actuator (69% of the dose leaving the spacer)¹³ is greater than that of BUD administered by means of the Turbuhaler (30% of the nominal dose)¹⁴ by using the Andersson sampler. However, because the devices are different, it is not possible to directly compare the respirable fraction, and unfortunately there are no in vivo data directly comparing these devices in terms of lung delivery.

The patients in our study were given both corticosteroids with twice daily dosing for 3 days and therefore should have reached steady-state tissue and blood drug levels. The plasma elimination half-life (BUD, 2.3 hours vs TAA, 3.6 hours)^{9,10} and the lipophilicity (BUD twice that of TAA)^{15,16} will determine intravascular and tissue accumulation, respectively. The similar pharmacokinetic profiles for TAA and BUD probably explain why there was no significant difference in systemic activity.

The importance of ensuring steady-state blood drug levels is that adrenal suppression is directly related to blood drug concentration. It is worth noting that 3 days is sufficient for steady-state systemic tissue concentration, and therefore effects of adrenal suppression, osteocalcin, and eosinophils can be reliably measured after such time. For the same reason, 3 days is sufficient to reduce plasma drug levels to negligible amounts, and therefore the systemic markers will return to baseline as evidenced by the nonsignificant difference between the first and second placebo values. This duration of treatment, however, is not sufficient to detect differences in antiasthmatic activity, and hence clinical efficacy was not intended to be an end point in this study. In fact it was more important for our patients to have an unchanged degree of asthma severity throughout the study because alterations in airway caliber might conceivably have altered lung bioavailability¹⁷ and added a potentially confounding variable to our results.

Because both of the corticosteroids studied had a high degree of first-pass hepatic metabolism (89%),^{18,19} the overall systemic bioactivity will be determined mainly

by the lung bioavailability where there is no first-pass metabolism. There was negligible contribution from oral bioavailability because all of our patients practiced mouth rinsing after inhalation, which is the usual clinically recommended practice to avoid oral candidiasis. It is conceivable that individual differences in inhaler technique might have affected the systemic bioavailability, which is dependent on lung delivery. However, we tried to obviate this factor by regular checking of inhaler technique with the aide of training devices, and both the Turbuhaler and integrated spacer devices are designed to facilitate ease of administration. Another factor that would influence the systemic bioactivity is poor compliance. Therefore we also took great care to maximize correct timing and dosing of medication by issuing a clear instruction sheet, keeping the dosing schedule short and simple, reinforcing compliance before and during the study, and analyzing compliance tick charts.

We also showed in this study that there was no significant dose-related suppression with any of the systemic markers used. Indeed, for all markers of HPA-axis activity, there was no significant difference between either treatment and placebo, even at the high dose of 1600 µg/day. These findings are in keeping with results from 2 of our previous dose-ranging studies, also performed with asthmatic subjects, in which neither BUD (500 µg to 2000 µg/day administered by means of a pressurized metered-dose inhaler)²⁰ nor TAA (400 µg to 1600 µg/day administered by means of an integrated spacer)²¹ exhibited a significant dose-response effect on 8 AM serum cortisol. Aarosen et al²² also showed no dose-response effect for budesonide (800 µg to 3200 µg/day) administered by means of Turbuhaler in terms of 8 AM cortisol or 250 µg cosyntropin stimulation test after 6 weeks of treatment in asthmatic patients. Moreover, in all of the above studies there was no significant difference between placebo and the highest dose of either BUD or TAA in terms of 8 AM cortisol. However, in healthy volunteers, BUD 1600 µg administered by means of the Turbuhaler produced a 47% reduction in 8 AM serum cortisol.²³ In this respect studies in healthy volunteers can be misleading because of potential differences in lung bioavailability caused by altered small airway caliber in asthmatic subjects.²⁴ This is illustrated in this study by a 34% reduction in mean FEF₂₅₋₇₅, a marker of small airway caliber.

Because it is known that patients differ in their response to inhaled corticosteroids, it is also important to look at the individual responses to inhaled corticosteroids, as well as the mean data. Our results showed no significant difference in the number of individual low values for both 8 AM serum cortisol (<5.4 µg/dL or 150 nmol/L) or overnight urinary cortisol (<3.6 µg or 10 nmol) between inhaled BUD or TAA at all doses. In this respect it is known that patients who have an abnormally low value for 8 AM serum cortisol and urinary free cortisol excretion while receiving inhaled corticosteroid medication also exhibit a subnormal dynamic response to adrenocorticotrophic hormone stimulation.²⁵⁻²⁷ Unfortunately, we were unable to evaluate the adrenocorticotrophic hormone stimulation response in our

study, because it is contraindicated in the UK data sheet (Synacthen, Novartis, UK) for use in asthmatic or atopic subjects because of occasional reports of potentially fatal anaphylactic reactions.

Although there was no significant dose-related suppression for blood eosinophils and serum osteocalcin, there was significant suppression of these 2 parameters for both drugs compared with placebo at the highest dose. In general it is assumed that the suppression of these 2 markers is less sensitive than that of adrenal suppression.⁵ However, different studies have previously shown blood eosinophil suppression to be more sensitive than cortisol suppression with inhaled²⁸ and intranasal²⁹ corticosteroids. In addition, Knutsson et al³⁰ reported a 53% suppression in 8 AM serum osteocalcin but only a 26% fall in 8 AM serum cortisol after 1 week of intranasal BUD 400 µg/day. Osteocalcin is a sensitive marker of the function of osteoblasts but is only a surrogate marker for overall effects of bone turnover and is therefore not as clinically valid as bone densitometry, which is considered the gold standard.⁵ Another potential reason for lack of detectable systemic bioactivity in terms of cortisol suppression was that the HPA axis had not recovered from previous corticosteroid use. However, this would be unlikely in this study because no patient usually received a maintenance dose greater than that used in the study, and both placebo values (after washout) were within normal limits.

In conclusion, we have shown that there was no evidence of overall dose-related suppression with either inhaled BUD or TAA by using 3 sensitive markers of HPA-axis activity (8 AM serum cortisol, overnight urinary cortisol excretion, and overnight corrected cortisol/creatinine ratio) and with osteocalcin and blood eosinophil count. There was no significant difference between these 2 drugs within a dose range of 400 µg to 1600 µg/day. Compared with placebo, there was significant suppression of osteocalcin and blood eosinophils, which occurred only at the highest dose levels of both drugs.

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