

Effect of nasal triamcinolone acetonide on lower airway inflammatory markers in patients with allergic rhinitis

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Asthma, rhinitis,
other respiratory
diseases

Background: Allergic rhinitis (AR) and asthma are commonly associated, and similar underlying inflammatory processes link both diseases. AR, even in the absence of asthma, is associated with increased levels of exhaled nitric oxide (ENO) and hydrogen peroxide (H_2O_2) in exhaled breath condensate, 2 noninvasive markers of lower airway inflammation.

Objective: We sought to evaluate the effect of treatment with the nasal steroid triamcinolone acetonide on ENO and exhaled H_2O_2 in subjects with AR.

Methods: We allocated 23 subjects in a randomized, double-blind, parallel-controlled fashion to 4-week treatment with triamcinolone acetonide (220 μ g/d) or matching placebo.

Results: ENO levels were greater in the subgroup with concomitant asthma (16/23 subjects) and decreased significantly with triamcinolone acetonide treatment in this subgroup of patients in comparison with patients receiving placebo. Breath condensate levels of H_2O_2 were higher in patients with AR without asthma than in those with asthma but decreased significantly with triamcinolone acetonide treatment in both subgroups. No changes were observed in bronchial hyperresponsiveness, nasal and asthma symptoms, or peak expiratory flow with active treatment or placebo.

Conclusion: We conclude that treatment of AR with triamcinolone acetonide results in decrease of 2 noninvasive markers of lower airway inflammation, ENO and H_2O_2 , supporting that upper and lower airway inflammation should be seen as a continuum in subjects with AR with and without asthma. ENO might be a more specific marker of the lower airway inflammation present in asthma. (*J Allergy Clin Immunol* 2003;111:313-20.)

Key words: Breath tests, triamcinolone, airways, inflammation, asthma, rhinitis

Upper and lower allergic airway inflammation are strongly associated. It has been estimated that 60% to 80% of patients with asthma have concomitant allergic rhinitis (AR),¹ and up to 40% of patients with AR have clinically

Abbreviations used

AR:	Allergic rhinitis
BHR:	Bronchial hyperresponsiveness
ENO:	Exhaled nitric oxide
NasNO:	Nasal nitric oxide
NO:	Nitric oxide
NOS:	Nitric oxide synthase

demonstrable asthma.² Both conditions have similar underlying pathogenesis and immunologic mechanisms.³ AR without overt clinical symptoms of asthma might be associated with bronchial hyperresponsiveness (BHR)⁴ and bronchial eosinophilia.^{5,6} In addition, eosinophilia of the nasal mucosa has been demonstrated in asthmatic patients with and without nasal symptoms.⁷ A recent report has shown that rhinitis is an important independent risk factor for asthma (adjusted odds ratio = 3.21).⁸

Exhaled nitric oxide (ENO) is considered a marker of lower airway inflammation, being increased in patients with asthma and decreased with anti-inflammatory treatment. ENO is also increased in atopic patients, even in the absence of asthma.^{9,10} Atopic patients with rhinitis have higher levels of ENO when compared with nonatopic patients.¹⁰ ENO is increased in patients with AR during the nonpollen season, increasing further during the pollen season.¹¹ Significant correlations have been found among increased ENO levels and skin prick test scores,¹² total IgE levels,¹³ and blood eosinophilia⁹ in atopic patients. Nitric oxide (NO) production is modulated by nitric oxide synthase type 2 (NOS2) in inflammatory diseases. Expression of NOS2 in the airways is regulated in part by cytokine release, including IL-1 β , TNF- α , and IL-4, modulatory mediators thought to be involved also in nasal allergic inflammation. Hydrogen peroxide (H_2O_2), a marker of airway inflammation and oxidative stress, has recently been reported to be increased in the exhaled breath condensate of subjects with AR without asthma.¹⁴

Treatment of allergic inflammation in the nose with topical steroids reduces asthma symptoms and airway hyperresponsiveness.¹⁵ Mindful of these observations, we undertook the present study on markers of lower airway inflammation after treatment of AR with nasal triamcinolone. In addition to monitoring ENO and H_2O_2 in breath condensate, we evaluated the effect of triamcinolone acetonide on airway hyperresponsiveness.

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TABLE I. Subject characteristics

	Allergic rhinitis
N	23
Age*	37.9 (11.53)
Sex	16 F/7 M
Atopy	23
Seasonal allergens only	3
Perennial allergens only	9
Seasonal and perennial allergens	11
No. of positive wheal reactions*	4.9 (3.7)
Duration of AR diagnosis (y)*	18.7 (10.5)
Coexistent asthma (n)	16
Duration of asthma diagnosis (y)*	17.81 (11.6)

*Mean ($\pm$ SD).

METHODS

Subjects

We recruited adults (aged 18-65 years) with AR from the Asthma and Airway Centre of the Toronto Western Hospital and by means of advertisements in flyers, newspapers, and magazines. The study protocol was reviewed and approved by the University Health Network Research Ethics Board. The diagnosis of coexisting asthma did not exclude patients from the trial unless they were using more than inhaled short-acting β_2 -agonists as needed for their asthma, had an FEV₁ value of 70% or less of predicted value after withholding short-acting bronchodilator for at least 6 hours, or were clinically unstable.

Subjects were not included in the study unless they had positive allergy skin test responses to one or more environmental allergens and had ENO levels of 20 ppb or greater. Subjects with troublesome nasal symptoms that interfered with daily activities or with sleeping at the time of the study or that were using or had used nasal, oral, inhaled, or intramuscular corticosteroids during the last 4 weeks before the recruitment were excluded. No other medication for treatment of AR or asthma, except for short-term β_2 -agonists, were allowed during the study. Upper respiratory tract infection, sinus infection, or asthma exacerbation within 4 weeks of recruitment or during the study were considered exclusion criteria. Current smokers and former smokers who have consumed cigarettes within the previous year or who had a lifetime tobacco consumption of greater than 10 pack-years were excluded.

Study design

After an initial screening visit, subjects participated in a 1-week run-in period when nasal and asthma symptoms, frequency, and amount of use of short-term β_2 -agonist and peak expiratory flow were recorded. Patients were re-evaluated at the end of this run-in period and, if stable, were allocated in randomized, double-blind, placebo-controlled parallel fashion to a 4-week treatment period with once daily triamcinolone acetonide (2 sprays per nostril of 55 μ g Nasacort AQ, Aventis Pharma) or matching placebo. Patients returned for assessment at the end of the treatment period. ENO and nasal nitric oxide (NasNO) were measured, followed by breath condensate collection and methacholine challenge testing before and after treatment. Symptoms, β_2 -agonist use, and peak expiratory flow values were recorded in the last week of treatment. The bottles of nasal medication were collected at the end of completion of the trial, and compliance was estimated from the liquid volume remaining.

Measurements

Measurement of ENO and NasNO were done according to American Thoracic Society recommendations¹⁶ by using a rapid linear-response chemiluminescent analyzer (Sievers 280, Boulder, Colo). For ENO measurements, subjects were asked to inhale air containing less than 5 ppb of NO through a mouthpiece connected to a 2-way valve to their total lung capacity over 2 to 3 seconds and then to exhale immediately. No nose clips were used. During the expiration, subjects maintained a constant pressure of 20 cm Hg displayed to them on the dial of a pressure gauge, resulting in velum closure, to avoid nasal contamination. A low expiratory flow rate of 0.046 L/s was used, which was produced by placing a high resistance in the expiratory limb. NasNO was measured by using a transnasal flow rate obtained by aspirating the air coming from one naris to the other during breath holding.¹⁶ The transnasal flow ranged from 3 to 6 L/min. NasNO levels were expressed as NasNO output (product of the used transnasal flow and NasNO concentrations obtained). The exhaled breath condensate was collected with a breath condenser (Cryocond; Boehringer Ingelheim, Burlington, Ontario, Canada) that cools and freezes the exhaled air to -30°C while patients breathe at tidal volume while wearing a nose clip for 5 minutes. Frozen samples were stored at -70°C . H₂O₂ was measured as described previously.¹⁷ The methacholine challenge test was performed according to American Thoracic Society guidelines.¹⁸

Statistical analysis

The unpaired *t* test (for normally distributed data) and the Mann-Whitney rank sum test (for non-Gaussian data) were used to compare treatment outcomes (changes from baseline) between placebo and triamcinolone acetonide. Correlations between baseline values and the magnitude of changes with treatments were assessed by means of the Spearman correlation coefficient test. The null hypothesis was rejected at a *P* value of less than .05. Values were expressed as means $\pm$ SD and medians (25th-75th percentiles) for normal and nonnormal distributed variables, respectively.

RESULTS

Twenty-four adults with AR were included in the study. One patient moved from Toronto before completion of the study. Therefore 23 patients (16 female and 7 male patients; mean $\pm$ SD age, 37.9 ± 11.5 years) were studied and were included in the analysis. Sixteen subjects had coexistent mild asthma. The demographic characteristics of all participants are summarized in Table I. Eighteen subjects (16 with coexistent AR and asthma and 2 with AR without asthma) demonstrated airway hyperresponsiveness (PC₂₀ <8 mg/mL), with a mean $\pm$ SD PC₂₀ value of 2.26 ± 1.9 mg/dL. Five subjects did not react to methacholine challenge (maximum dose given = 16 mg/mL). For the purposes of the study, subjects were considered to have asthma only if they had a clinical history of compatible symptoms and a significant response to methacholine; that is, the 2 subjects with asymptomatic bronchial hyperreactivity were not considered to have asthma for the purpose of the analysis. Subjects with AR and coexistent asthma had lower FEV₁ values (in liters) and FEV₁/forced vital capacity ratios when compared with those of subjects with AR but without asthma (*P* = .026 and .033, respectively; Table II). ENO levels were higher in patients with coexistent asthma when compared with those of patients without asthma (*P*

TABLE II. Baseline measurements (n = 23)

	Allergic rhinitis			P value*
	All patients (AR)	AR with asthma	AR without asthma	
No.	23	16	7	
ENO (ppb)	47.67 (30.64-78.17)	65.34 (45.67-81.17)	29.57 (24.93-34.51)	.021
H ₂ O ₂ (μmol/L)	3.5 (3.07-4.56)	3.28 (2.91-3.86)	5.46 (3.82-7.93)	.015
NasNO output	518.55 (138.21)	518.43 (157.76)	518.83 (88.44)	.99
FEV ₁ (L)	3.10 (0.98)	2.81 (0.73)	3.77 (1.20)	.026
FEV ₁ (% predicted)	94 (13.8)	90 (12.5)	101 (14.2)	.075
FEV ₁ /FVC	79 (6.4)	77 (5.9)	83 (6.1)	.033
FEV ₁ /FVC (% predicted)	94 (7.3)	92 (5.7)	100 (7.8)	.010

Values are expressed as mean (±SD) or median (25th-75th percentile) as shown.

FVC, Forced vital capacity.

*Comparison of baseline values between subgroups of patients with AR with asthma and those with AR without asthma were done with *t* tests (mean ± SD) and Mann-Whitney rank sum tests (median [25th-75th percentile]).

TABLE III. Characteristics and baseline values of subjects in each treatment group

	Triamcinolone acetonide	Placebo	P value*
No.	11	12	—
Age	39.16 (11.47)	36.63 (12.02)	.61
Sex	9 F/2 M	8 F/4 M	—
Time diagnosis of AR	18 (15.2-20)	18 (7.5-25)	.76
ENO (ppb)	53.33 (27.4-79.9)	47.10 (36.7-76.7)	.83
NasNO output (nL/min)	523.98 (468.01-574)	516 (360-652.5)	.88
H ₂ O ₂ (μmol/L)	4.83 (2.4)	3.78 (1.7)	.25
PC ₂₀ (n = 9)	2.59 (2.1)	1.91 (1.8)	.48
FEV ₁ (L)	3.22 (1.2)	3 (0.8)	.6
FEV ₁ (% predicted)	98.5 (14.1)	96.7 (12)	.75
FEV ₁ /FVC	80.1 (6.9)	77.8 (6)	.4
FEV ₁ /FVC (% predicted)	95 (7.9)	93 (6.9)	.49
Nasal symptom score	20 (11.5-7)	11.5 (7-13.5)	.06
AR with asthma (n)	7	9	—
Time diagnosis of asthma	20.85 (12.32)	15.44 (11.2)	.38

Values are shown as mean (±SD) and median (25th-75th percentile) as shown.

FVC, Forced vital capacity.

*Comparison of baseline values was done with *t* tests (mean ± SD) and Mann-Whitney rank sum tests (median [25th-75th percentile]).

= .021, Table II). H₂O₂ levels were higher in the participants with AR who did not have asthma in comparison with levels in the asthmatic subjects with AR (*P* = .015, Table II). Twelve patients received placebo, and 11 patients received triamcinolone acetonide. No significant differences in baseline measurements between the 2 treatment groups were observed (Table III).

Exhaled NO

A trend for decrease in ENO levels resulting from intranasal triamcinolone acetonide treatment (−6.63 ppb) was detected in comparison with that seen with placebo (7.54 ppb) when the group of patients with AR were analyzed as a whole (*P* = .069). In the subgroup of subjects with coexistent asthma, ENO levels decreased significantly with triamcinolone acetonide treatment but were not affected by placebo treatment (mean changes in ENO were −12.05 ppb with triamcinolone acetonide therapy and 10.6 ppb with placebo, *P* = .029). Pretreatment and posttreat-

ment median values of ENO are shown in Fig 1. The different response of the 2 subgroups (AR with asthma and AR without asthma) was confirmed by means of interaction treatment group analysis (*P* = .018). No significant difference between the baseline values between the 2 treatments in this subgroup was detected (*P* = .83). The median (25th-75th percentile) of baseline ENO values was 63.7 ppb (46.2-82.3 ppb) and 67 ppb (34.1-79.9 ppb) for placebo and triamcinolone acetonide treatments, respectively.

Hydrogen peroxide

Triamcinolone acetonide significantly decreased the concentration of H₂O₂ in the breath condensate of subjects with AR when compared with concentrations after placebo (mean difference from baseline with intranasal triamcinolone acetonide was −1.57 μmol/L, and that with placebo was 0.59 μmol/L, *P* = .006). Fig 2 shows pretreatment and posttreatment mean values of H₂O₂. H₂O₂ did not change significantly with either treatment in the

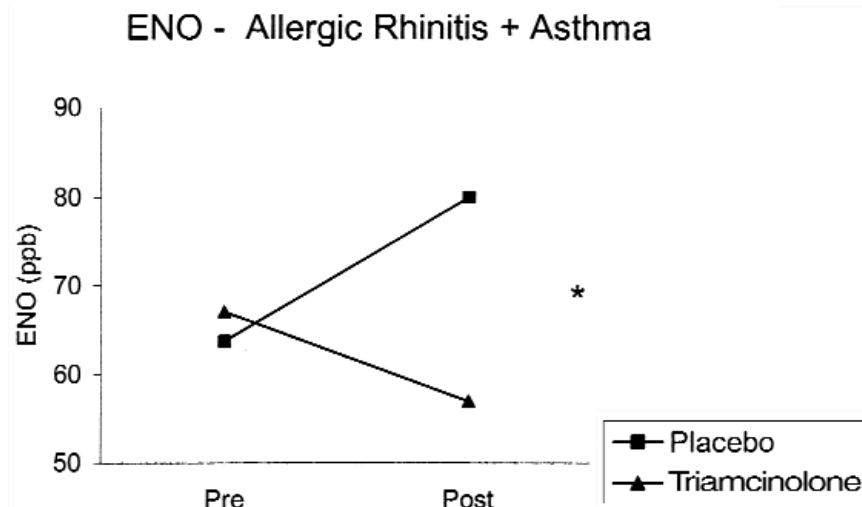


FIG 1. Pretreatment and posttreatment median ENO values. * $P = .029$ for comparison of mean differences from baseline between placebo (10.6 ppb) and triamcinolone acetate (−12.05 ppb) in subjects with AR and coexistent asthma.

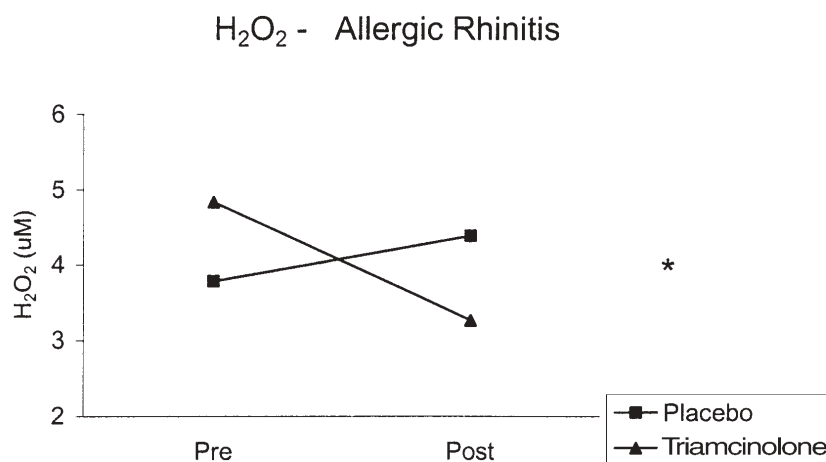


FIG 2. Pretreatment and posttreatment H₂O₂ mean concentration (in micromoles per liter). * $P = .006$ for comparison of mean differences from baseline between placebo (0.59 ppb) and triamcinolone acetate (−1.57 ppb) in subjects with AR with and without coexistent asthma.

subgroup with AR and asthma. Mean changes were $-0.34 \mu\text{mol/L}$ for triamcinolone acetate and $0.4 \mu\text{mol/L}$ for placebo ($P = .09$).

Airway hyperresponsiveness

Nine patients in the placebo group and 9 patients in the triamcinolone acetate group demonstrated BHR ($\text{PC}_{20} < 8 \text{ mg/mL}$). All hyperresponsive subjects in the placebo group and 7 of the 9 hyperresponsive subjects in the triamcinolone acetate group had asthma. The ratio between posttreatment and pretreatment PC_{20} was calculated for each treatment group, and comparison between groups was done with the t test. There was no significant difference in airway hyperresponsiveness with triamcinolone acetate (1.28) or placebo (1.04) treatment for subjects with AR ($P = .55$). The comparison of posttreat-

ment and pretreatment PC_{20} ratios between groups was performed in the subgroup of subjects with coexistent asthma, and no significant difference between changes resulting from placebo (1.04 ± 0.9) and triamcinolone acetate (1.18 ± 0.8) treatment was observed ($P = .75$).

NasNO output and nasal score

No significant changes were detected in NasNO levels with placebo or triamcinolone acetate treatments. The mean $\pm$ SD changes from baseline observed were $-10.26 \pm 159.9 \text{ ppb}$ for the placebo group and $-17.7 \pm 157.5 \text{ ppb}$ for the triamcinolone acetate group (total difference = 7.46 , $P = .91$).

A nearly significant trend for reduction in nasal symptoms score with triamcinolone acetate was observed, but the differences between treatments did not reach con-

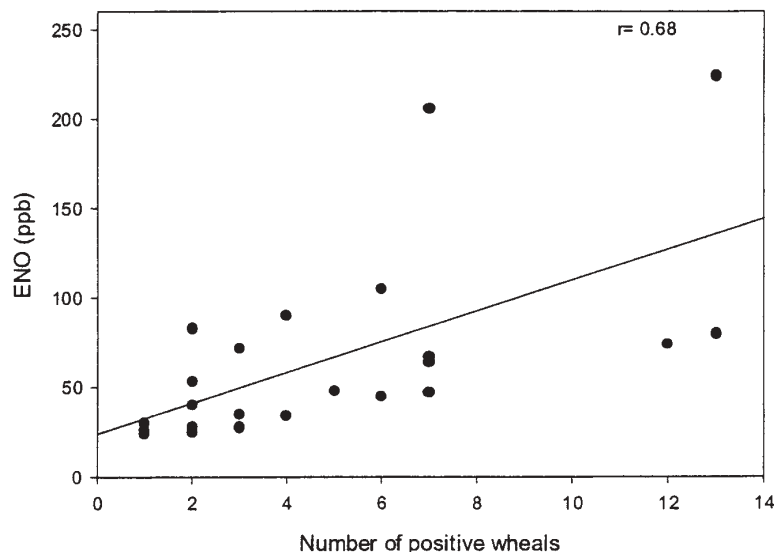


FIG 3. Correlation between the number of positive wheal reactions and baseline ENO levels.

ventional levels of statistical significance (total difference = 18.6, $P = .06$). Mean $\pm$ SD differences from baseline in nasal score occurring after administration of placebo and triamcinolone acetonide were 8.41 ± 28.4 ppb and -10 ± 13.2 ppb, respectively.

Asthma outcomes

FEV₁ in patients with coexistent asthma and AR was unaffected by triamcinolone acetonide (0.054 L) or placebo (-0.001 L) treatments ($P = .67$). Similarly, no changes in asthma symptom scores (median changes were 2 for triamcinolone acetonide and 1 for placebo, $P = .63$), bronchodilator use (median changes were 0 for both treatments, $P = .91$), or peak flow levels (median changes were 0 for both treatments, $P = .24$) were observed.

Correlations

Baseline ENO levels correlated positively with the number of positive wheal reactions ($r = 0.68$, $P < .001$; Fig 3). No significant correlations between changes in H₂O₂ and ENO levels with intranasal triamcinolone acetonide treatment were detected.

Compliance

The volume of medication left in the bottles was measured, and the compliance with the study medications was evaluated. There was no significant difference in compliance between the 2 treatment groups ($P = .86$). The mean $\pm$ SD compliance was $72\% \pm 20.8\%$ in the placebo group and $74\% \pm 20.1\%$ in the triamcinolone acetonide group. One patient in the placebo group returned the bottle with less volume than expected. When this patient was excluded from the analysis, the median compliance for the placebo group was 68% ($P = .51$). Compliance did not correlate with changes in ENO levels ($r = -0.3$, $P = .3$) or breath condensate H₂O₂ concentration in patients receiving triamcinolone acetonide ($r = 0.1$, $P = .6$).

DISCUSSION

We have shown that treatment of AR with the intranasal steroid triamcinolone acetonide reduces evidence of lower airway inflammation as expressed by 2 inflammatory markers, ENO and H₂O₂. Our findings support the concept that there is an important link between upper and lower airway inflammation in patients with AR. In addition, on the basis of the subgroup analysis, we were able to demonstrate that these 2 inflammatory markers behave differently under intranasal steroid therapy in patients with AR, depending on whether asthma coexists. ENO decreased significantly with nasal corticosteroid therapy only in the subgroup of patients with AR and coexistent asthma, whereas H₂O₂ was reduced in the group of patients with AR as a whole. Our finding that patients with AR and asthma had higher baseline levels of ENO than patients with AR without asthma confirms previous findings in our laboratory. ENO levels correlate with IgE levels and, as demonstrated by this and previous studies, with the number of positive skin test wheal reactions.^{12,13,19} Others have reported that ENO is higher in atopic asthma in comparison with nonatopic asthma,^{10,20,21} suggesting that atopy and asthma influence ENO levels independently. The differences in ENO baseline levels and in the response of ENO to steroid therapy when the presence of asthma was taken into account support this. Gratziau et al¹⁰ demonstrated that levels of ENO in subjects with rhinitis did not differ from the levels of ENO in subjects with asthma or subjects with asthma and concomitant rhinitis. Their results are not directly comparable with ours because they included patients with and without atopy in all subgroups. Henriksen et al¹⁹ have evaluated 431 adolescents with different clinical phenotypes (involving asthma and AR) randomly selected from a large-scale epidemiologic survey. The authors demonstrated that for ENO there was

a continuous increase from the lowest values in the nonasthmatic subjects with AR and negative BHR to the highest values in asthmatic patients with AR. No significant difference was found between the group with AR and asthma and the groups with AR (with and without BHR). The group with AR and no BHR had lower levels of ENO than the group with AR and BHR. The relatively small number of patients with AR without asthma in our study precluded within-group subanalyses concerning BHR. However, a previous study done in our laboratory demonstrated that hyperresponsive atopic subjects did not differ significantly from nonhyperresponsive atopic subjects in regard to ENO levels.¹²

Several studies have reported the inhibitory effect of lower airway inhaled steroids on ENO in patients with asthma, but to our knowledge, no previous study has looked at the effects of nasal steroids on ENO or breath condensate H_2O_2 in patients with AR with or without asthma. We do not think that reduction of ENO is the direct consequence of nasal corticosteroid spilling into the lower airway. In a previous study with intranasal radio-labeled beclomethasone dipropionate, less than 2% of the total radioactivity was detected in the chest after nasal administration.¹⁵ Because of the low systemic bioavailability of nasal triamcinolone acetonide, it is unlikely that our findings are the result of a systemic action of this compound. It is probable that the inhibitory effect of nasal triamcinolone on ENO levels and on H_2O_2 concentration is related to the anti-inflammatory properties of steroids on cytokines and inflammatory cells that are involved with ENO and H_2O_2 production rather than with a direct inhibitory effect on NOS2. A recent study further supports this assumption by failing to demonstrate regulation of NOS2 expression by steroids in human epithelial cells.²² Our study showed a statistically significant effect of nasal triamcinolone on ENO in subjects with asthma but failed to demonstrate a statistically significant effect in subjects without asthma. We cannot rule out the possibility that there is a small effect in subjects without asthma and that such an effect might have been demonstrable in a larger number of subjects.

Patients with AR have increased levels of H_2O_2 detected in the breath condensate when compared with levels in healthy control subjects.¹⁴ Eosinophils seem to be the main source of H_2O_2 in mild asthma.²³ Because eosinophilic inflammation plays a significant role in AR,⁴⁻⁶ it is not surprising that increased levels of H_2O_2 are also found in these patients. Ogasawara et al²⁴ have demonstrated previously that eosinophils present in nasal secretion generate H_2O_2 in response to allergen challenge in patients with AR, supporting the relationship between increased production of H_2O_2 by eosinophils in these patients. In their study, blood eosinophil numbers increased after the nasal challenge and were related with IgE levels. In our study we detected a higher baseline concentration of H_2O_2 in the subgroup without asthma in comparison with the subgroup with concomitant asthma, which is opposite to our findings for ENO. The differences between these inflammatory markers in asthma and AR warrant further study. The discor-

dance between changes in ENO and changes in H_2O_2 with nasal steroid treatment suggests that these 2 markers reflect different aspects of the lower airway inflammation. Ferreira et al²⁵ have reported discordant response between ENO and breath condensate H_2O_2 in patients with chronic obstructive pulmonary disease treated with lower airway inhaled beclomethasone.

We cannot rule out the possibility that some of the breath condensate H_2O_2 measured in our study was of upper airway origin. We think that this is unlikely, however. Breath condensate H_2O_2 levels parallel lower airway H_2O_2 levels in the lower airway in intubated patients in whom the upper airway has been bypassed as a source of contamination.²⁶ Moreover, exhaled breath condensate H_2O_2 levels correlate with several sputum^{23,27} and serologic markers of inflammation.²⁸ Finally, exhaled breath condensate H_2O_2 concentrations are influenced by expiratory flow rates,²⁹ which is strong indirect evidence that the H_2O_2 being measured is of lower airway origin. Similarly, there is little evidence that breath condensate is contaminated by passage through the mouth. For example, Effros et al³⁰ have shown that the average amylase concentration in the condensate is less than 0.01% of that in saliva.

Previous investigations have demonstrated the inhibitory effect of lower airway inhaled steroids on H_2O_2 in patients with asthma. Antczak et al³¹ have recently shown that treatment with inhaled chlorofluorocarbon-free beclomethasone dipropionate reduces the levels of H_2O_2 in the breath condensate of subjects with moderate asthma. Previous cross-sectional studies had demonstrated that H_2O_2 concentration is lower in the breath condensate of asthmatic patients taking inhaled steroids in comparison with steroid-naïve patients.²⁷

Corroborating some studies in the literature,^{32,33} but not others,^{34,35} we have not detected significant changes in NasNO levels, as expressed by NasNO output, with intranasal triamcinolone acetonide treatment when compared with that with placebo. Wilson et al³³ also failed to demonstrate a decrease in NasNO levels in patients with AR treated with mometasone furoate.³³ Similarly, Gratzou et al³² did not detect changes in NasNO with the combined treatment with inhaled and nasal steroids. In contrast, Baraldi et al³⁵ studied children with perennial AR and demonstrated that therapy with beclomethasone decreased the levels of NasNO. However, all children in this study were allergic to house dust mites. Subjects exposed to perennial allergens are more likely to have higher upper and lower airway inflammation caused by constant exposure and might therefore demonstrate more clearly a response to anti-inflammatory treatment. NasNO and ENO are greater in subjects sensitized for house dust mite in comparison with other allergens³⁶ and independently and positively related to the severity of house dust mite reactivity.³⁷ We included patients with seasonal and perennial AR, and Wilson et al³³ included patients with seasonal AR. Therefore different methodologies in sensitization might have accounted for the differential results. Additionally, our study was not powered for detecting changes in secondary outcomes, and a large-

er number of subjects might have been necessary to detect changes in NasNO output. We failed in demonstrating significant changes in BHR with triamcinolone acetonide, which might suggest that BHR was less sensitive in detecting changes in the lower airway inflammation in comparison with ENO and H₂O₂. Although they used a different study design, Pelucchi et al³⁸ have shown that treatment with nasal beclomethasone did not inhibit the increase in bronchial responsiveness during the pollen season, although it decreased the number of eosinophils in nasal lavage fluid in patients with AR. In contrast to such findings, Watson et al¹⁵ demonstrated a significant improvement in BHR to methacholine, with a change in PC₂₀ from 1.8 to 3.3 mg/mL after 4 weeks of treatment with beclomethasone dipropionate in a randomized, double-blind, placebo-controlled, crossover study. One explanation for this apparent discrepancy between studies is that all patients in the study by Watson et al were sensitive to perennial allergens, more potent stimuli of upper and lower airway inflammation. Our inability to show changes in BHR, as well as asthma, symptoms might be explained as well by the very mild asthma in our study population. We note also that our study of triamcinolone was done independently of season; the effect of therapy might have been less evident in patients studied out of season.

In summary, we have demonstrated, in this study, that treatment with a nasal steroid reduces lower airway inflammation in patients with AR with and without asthma supporting the link between upper and lower inflammatory processes. ENO and H₂O₂ reflect different aspects of the inflammation present in the airways with ENO relating more closely with the presence of asthma. Both inflammatory markers appear to be more sensitive than indirect means of assessment of airway inflammation, such as airway hyperresponsiveness.

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