

Treatment of Nasal Inflammation Decreases the Ability of Subjects with Asthma to Condition Inspired Air

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We previously showed that individuals with seasonal allergy have a reduced ability to condition air, which was improved by nasal inflammation. We also showed that subjects with asthma have a reduced ability to condition air. Because individuals with asthma usually have inflammation in the nose, we hypothesized that treatment with an intranasal steroid would reduce nasal inflammation and further decrease nasal conditioning capacity. We performed a randomized, double blind, placebo-controlled, 2-way crossover study on 20 subjects with asthma comparing the effect of treatment with intranasal budesonide for 2 weeks on nasal conditioning. Treatment with budesonide caused no significant effect on nasal conditioning as compared with placebo. When we evaluated the subgroup of nonsmoking subjects, budesonide caused a significant reduction in nasal conditioning. We speculate that nasal inflammation in non-smoking individuals with asthma increases the conditioning capacity and reducing it with an intranasal steroid worsens the ability of the nose to condition air. In addition, smoking causes an increase in nasal conditioning capacity by non-steroid-dependent factors. These observations help us understand the pathophysiology of nasal conditioning, but do not negate the positive clinical benefits of budesonide on treating nasal inflammation.

Keywords: asthma; intranasal steroids; nasal conditioning; smoking

A major function of the nose is to warm and humidify air (1). We have developed a method of using inhalation of cold, dry air (CDA) to evaluate the ability of the nose to condition air (2). We previously showed that subjects with seasonal allergic rhinitis, out of their allergy season, had a reduced ability to warm and humidify air compared with normal subjects (2). In contrast, subjects with seasonal allergy with allergic inflammation induced by either seasonal exposure or antigen challenge have an increased ability of the nose to condition inspired air (3). Subjects with asthma subjects have a significantly reduced ability to condition air as compared with normal subjects (4). The mechanisms underlying the physiologic differences in conditioning capacity has not been elucidated.

Intranasal corticosteroids are effective drugs widely used to treat allergic rhinitis as well as a number of other inflammatory disorders (5, 6). Inhaled corticosteroids are effective agents in the treatment of asthma. The inflammation in the nose of subjects with asthma is probably similar to the inflammation in their lungs and should respond to local steroid application (7, 8). Because we have previously shown that allergic inflammation

increases the ability of the nose to condition air, we hypothesized that treatment of nasal inflammation in asthmatic subjects with intranasal steroids would decrease nasal conditioning. Our goal was to test whether reducing inflammation in the nose would worsen the conditioning capacity of asthmatics, making our previously observed differences between asthmatics and normal subjects even more pronounced. Some of the results of these studies were previously presented (9).

METHODS

Subjects

We recruited 20 subjects with a physician's diagnosis of asthma (Table 1). Allergic status was documented by puncture skin tests. None of the above subjects were taking oral or intranasal medications within 2 weeks of the evaluation. The Institutional Review Board of the University of Chicago approved the study, and written informed consent was obtained from each subject.

Experimental Protocol

We performed a randomized, double-blind, placebo-controlled, 2-way crossover study comparing the effect of 2-week treatment with budesonide (AstraZeneca, Wilmington, DE) or placebo solution on nasal conditioning capacity. The protocol for the visit was shown in Figure 1. The measurement of nasal conditioning was done as described previously (2), but was modified to shorten the time at each flow rate to 12 minutes.

The difference between water content of air before entry into the nose and that in the nasopharynx is the water gradient (WG) across the nose; it represents the amount of water evaporated by the nose to condition air, a measure of nasal conditioning. The total WG represents the sum of the WGs obtained at each flow rate.

Symptoms of runny and stuffy nose for each nostril and a combined sensation of itchy nose and throat were also recorded at each time point and graded on a scale as follows: 0 = no symptoms, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe symptoms.

Nasal volume measurement was performed with an Eccovision Acoustic Rhinometry System (Hood Laboratories, Pembroke, MA). The volume was measured between 0 and 6 cm from the tip of the rhinometry probe. Each measurement was performed in triplicate, and the average values are reported.

A nasal probe developed for measurement of mucosal surface temperature was calibrated before each use (2). Measurement of nasal mucosal temperature during exposure to cold, dry air was performed by advancing of the temperature sensor attached to a small, straight rod through a small opening in the mask.

Secretions were collected from the anterior nasal septum by use of filter paper discs as previously described (10).

Five milliliters of warmed (37°C) lactated Ringer's were instilled into each nostril and, after 10 seconds, the subjects expelled the lavage fluid into a plastic collection vessel. After the total cell count was obtained, the samples were centrifuged. Aliquots for eosinophil cationic protein and albumin determination were stored at -20°C until assayed. A differential count on the cell pellet was performed.

Eosinophilic cationic protein, a marker of eosinophil secretion, was measured by a double-antibody radioimmunoassay obtained from Pharmacia AB (Uppsala, Sweden). Human serum albumin was measured by an ELISA sensitive to 1 ng/ml of albumin.

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TABLE 1. DEMOGRAPHIC DATA FOR ALL SUBJECTS

No. of Subjects	20
Age, yr	
Mean	27
Median	26
Range	18–47
% Male	50
% Using inhaled steroids	50

Statistical Analysis

For the WG, statistical analysis was performed by use of parametric statistics (2, 11). For other parameters, nonparametric statistics were used for analysis. Repeated measurements were compared by the appropriate ANOVA, and post-hoc analysis was performed if indicated (11). *p* Values < 0.05 were considered significant.

RESULTS

Increasing the CDA flow rate progressively increased the WG with both budesonide and placebo treatment ($p < 0.001$ for each comparison versus 5 L/min) (Figure 2). At each flow rate and for the total WG, there was no difference between the budesonide and placebo treatment ($p > 0.05$ for all) (Figure 2).

To determine whether any of the physiologic parameters that could affect the WG might be influenced by budesonide treatment, we examined the effects of treatment on nasal volume, nasal mucosal temperature, symptom scores, and indices of inflammation.

Nasal volume after CDA exposure decreased compared with the baseline for both treatments ($p < 0.01$ each comparison). There were no significant differences in the reduction of nasal volume after CDA exposure between treatments ($p > 0.05$).

The nasal mucosal temperature decreased significantly from baseline after CDA in both treatments ($p < 0.001$). The nasal mucosal temperature measured at baseline after CDA exposure was not significantly different between treatments ($p > 0.05$ each

comparison). The net change in nasal mucosal temperature did not differ between treatments ($p > 0.05$).

Nasal secretion weights increased after both budesonide and placebo treatments after CDA compared with the value at baseline ($p < 0.001$ each comparison). There were no significant differences in the CDA-induced increase in nasal secretion weights between treatments ($p > 0.05$). The rhinorrhea and congestion scores increased significantly after CDA as compared with baseline ($p < 0.01$ each comparison). There were no significant differences in rhinorrhea or congestion scores between treatments ($p > 0.05$ all comparisons). Pruritus and sneezing scores did not increase after CDA and were not significantly different between treatments ($p > 0.05$ all comparisons).

The number of total cells and of eosinophils as well as the level of albumin in the nasal lavage fluid at baseline before CDA exposure were low and were not significantly different ($p > 0.05$ each) between treatments. Eosinophil cationic protein levels were detectable in only one subject.

We analyzed whether any demographic parameter might influence the effect treatment on response to treatment of the total WG. There were no significant differences in total WG when we accounted for age, sex, skin test score, response to any allergen (or dust specifically), use of inhaled steroids, or reported baseline symptoms during measurement ($p > 0.05$ all comparisons).

Our analysis showed an effect of cigarette use. Thus, we stratified our data by smoking status. The demographic characteristics of our subjects, stratified by smoking status (including amount of tobacco use), are shown in Table 2. There were no differences in baseline measures between smokers and nonsmokers (Table 2) ($p > 0.05$, all). However, we did detect a difference in the response to budesonide in nonsmokers. Compared with placebo, treatment with budesonide in nonsmokers resulted in a decrease in water gradient at the 20 L/min flow rate, and also for the total WG, whereas smokers showed no differences in WG treatments (Figure 3).

Examination of physiologic parameters in this subgroup showed that nasal volume after CDA exposure decreased compared with baseline with both treatments in both smokers and nonsmokers ($p < 0.05$ for each comparison); smokers showed a decrease in nasal congestion on probe insertion with budesonide ($p < 0.05$), but otherwise showed similar results (Figure 4). There were no significant differences in the reduction of nasal volume after CDA exposure between treatments at any time point in either smoking group ($p > 0.05$ for each comparison) (Figure 4). The nasal mucosal temperature measured at baseline was significantly lower on budesonide than on placebo in nonsmokers (mean $\pm$ SEM: $28.63 \pm 1.00^\circ\text{C}$, $31.20 \pm 1.03^\circ\text{C}$; $p < 0.05$); there was no difference in smokers (mean $\pm$ SEM: $29.55 \pm 0.92^\circ\text{C}$, $30.33 \pm 1.03^\circ\text{C}$; $p > 0.05$) (Figure 4). The nasal mucosal temperature decreased significantly from baseline after CDA in both treatments in smokers and nonsmokers ($p < 0.01$). The net change in nasal mucosal temperature did not differ between treatments in either group ($p > 0.05$).

There were no significant differences in the CDA-induced increase in nasal secretion weights between treatments in either group ($p > 0.05$). The rhinorrhea scores increased significantly after CDA compared with baseline in both treatments in nonsmokers ($p < 0.01$ each comparison). In smokers, there were similar increases, though these did not reach significance when compared after probe insertion in either treatment ($p > 0.05$ both). There were no significant differences in rhinorrhea scores between treatments in either nonsmokers or smokers ($p > 0.05$ all comparisons). Congestion scores increased after CDA compared with baseline ($p < 0.05$ each comparison); there were no differences between treatments ($p > 0.05$ all comparisons) in nonsmokers except that after probe insertion, scores were lower

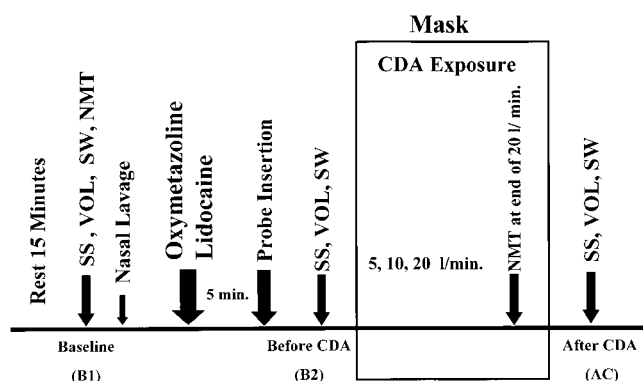


Figure 1. Experimental protocol. The different interventions and measurements are indicated by arrows; timing between these is reflected below arrows in the space between them. Measurements included symptoms scores (SS), nasal volume (VOL), nasal mucosal temperature (NMT), and secretion weight (SW); these were performed on the opposite side of the nasal vault containing the probe. The nasopharyngeal probe was inserted into one side of the nose selected randomly. Cold dry air (CDA) was delivered by mask at 3 flow rates (5, 10, and 20 L/minute) for 12 minutes each (depicted in the boxed area). The protocol is shown on the abscissa and is detailed in the text. B1 = baseline, B2 = after probe insertion, AC = after CDA.

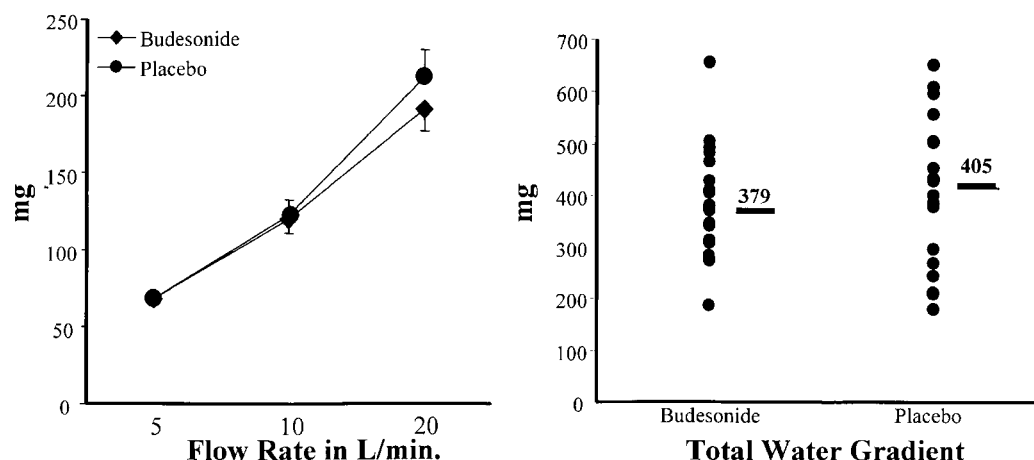


Figure 2. Effect of budesonide on water gradient in all subjects. *Left panel:* Water gradient across the nose at three flow rates (5, 10, 20 L/min). Data are mean $\pm$ SEM for 20 subjects. *Diamonds* = budesonide, *circles* = placebo. There was increased conditioning with increasing flow rate. There were no differences between treatments. *Right panel:* Individual data of total water gradient across the nose. The *solid bars* with the numbers above represent the mean of individual data points.

on budesonide (1, 0; $p < 0.05$) (Figure 5). In smokers, congestion scores also increased after CDA compared with baseline ($p < 0.05$), with no significant differences between treatments. Itching scores were not significantly different between time points in either treatment in either group ($p > 0.05$). However, they were significantly lower after probe insertion (1, 2; $p < 0.05$) and after CDA on budesonide in nonsmokers (1, 3; $p < 0.05$); smokers did not show any differences at any time point in either treatment ($p > 0.05$ all comparisons) (Figure 5). The net change in the itching score was not different across treatments in either group ($p > 0.05$). Sneezing scores did not change between time points in either treatment, and were not significantly different between treatments in either group ($p > 0.05$, all comparisons). The number of total cells and of eosinophils was not significantly different in either group ($p > 0.05$). Albumin in the nasal lavage fluid was significantly lower on budesonide in nonsmokers (mean $\pm$ SEM: 9.51 ± 2.81 , 26.38 ± 8.69 $\mu\text{g/ml}$; $p < 0.05$); it was not significantly different in smokers (8.90 ± 1.26 , 12.64 ± 3.48 $\mu\text{g/ml}$; $p > 0.05$) (Figure 6).

DISCUSSION

Our data show that in nonsmokers, an intranasal steroid, budesonide, decreased inflammation, as indicated by reduced vascular

leakage, and also decreased nasal conditioning. Smoking inhibited the response to the nasal steroid.

Although this study was done to better understand the physiology of nasal conditioning, it has clinical implications. Because the nose serves to initiate air conditioning for the respiratory tract, its dysfunction may negatively affect the lower airway. Annesi and colleagues showed that subjects reporting nasal sensitivity to CDA had a more rapid decline in FEV₁ over 5 years than did those without such sensitivity (12). Inhalation of the same volume of dry air through the mouth, in contrast to the oronasal route, causes a greater reduction in FEV₁ in subjects with asthma (13–14). In addition, prolonged repeated exposure of the airways to inadequately conditioned air can induce inflammation in the lower airway (15). Mice lacking the aquaporin 5 (*Aqp5*) gene, a major water channel that is expressed in the airway epithelium, have been shown to have increased bronchial hyperreactivity, suggesting that water transport may be an important process affecting asthma (16). The ultimate example is the histologic changes in the lower airway of patients undergoing a total laryngectomy. Based on these observations, we believe that the reduced nasal ability to condition air in individuals with asthma may modulate lower airway pathology.

Reducing allergic nasal inflammation with intranasal steroids, however, has many clinical benefits including positive effects on the lower airway (5, 6). On the other hand, we suspect that allergic inflammation increases water movement through the paracellular spaces or via actions on ion channels, explaining its beneficial effects on nasal conditioning. The observation that treating allergic inflammation with intranasal steroids would worsen nasal conditioning follows logically from their beneficial effects on reducing nasal allergic inflammation. Thus, we have a paradox in which an efficacious treatment for allergic rhinitis would have a negative impact on nasal conditioning. The observations are clear, but the resolution of the paradox is not. The benefits of reducing nasal inflammation on systemic or reflex-mediated effects on the lower airway probably exceed the negative effect on reducing the conditioning capacity of the nose in the majority of people. The important point is that the data support the hypothesis that allergic inflammation improves nasal conditioning.

It is interesting to speculate that the local irritation from intranasal steroids may result from decreasing water transport and increasing osmolarity of the secretions as the nose conditions air. Another relevant clinical finding is that the combination of a β -agonist and an inhaled steroid is more efficacious than doubling the dose of steroid in the treatment of asthma. β -Agonists

TABLE 2. DEMOGRAPHIC DATA STRATIFIED BY SMOKING

	Nonsmokers	Smokers
Number of subjects	11	9
Age, yr		
Mean	27	28
Median	27	22
Range	18–40	18–47
% Male	45	56
% Using inhaled steroids	36	67
Tobacco use, cigarettes/d		
Mean		5.7
Median		5
Range		1–15
Nasal temperature, °C	31.20	29.55
Nasal volume, cc	5.45	6.06
Total water gradient, mg	393.04	419.70
Albumin, $\mu\text{g/ml}$	26.4	8.9
Secretion weight, mg	8.34	2.91
Eosinophils, no.	3,239	325
Total cells, no.	19,797	9,568

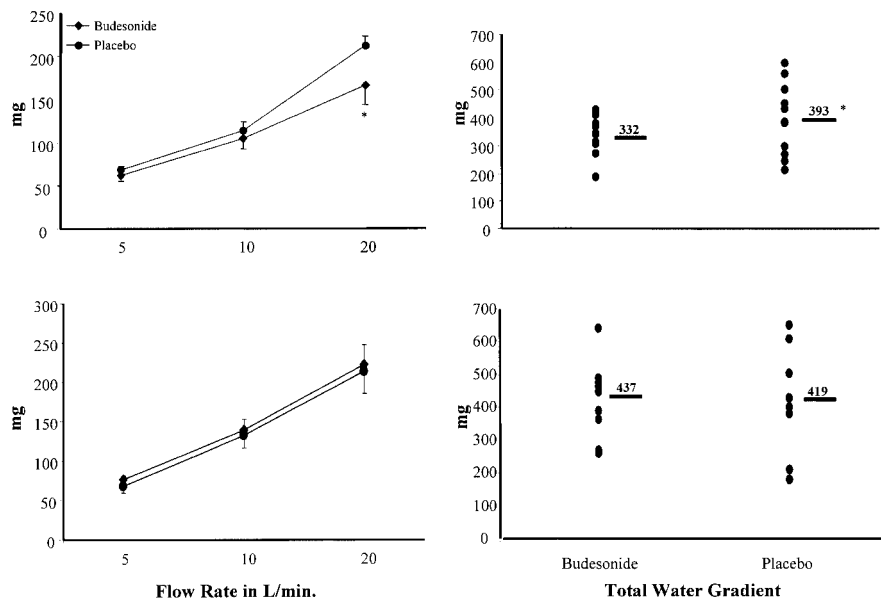


Figure 3. Effect of budesonide on water gradient in nonsmokers. *Left panels:* Water gradient across the nose at three flow rates (5, 10, 20 L/min). Data are mean $\pm$ SEM (11 nonsmokers above and 9 smokers below). *Diamonds* = budesonide, *circles* = placebo. *Right panels:* Individual data of total water gradient across the nose. The *solid bars* with the numbers above represent the mean of individual data points. Nonsmokers are shown above and smokers below. * $p < 0.05$.

increase ion and therefore water transport and could explain this clinical observation. Perhaps using a lower dose of intranasal steroid combined with an agent to increase water transport, other than cigarette smoke, would provide even greater clinical benefit in the treatment of allergic rhinitis. It should be noted that the dose of budesonide we chose for this study is the maximum recommended dose rather than the usually recommended starting dose, thus the strategy for this agent appears to be reducing symptoms without eliminating inflammation and possibly causing adverse effects. In summary, there are important theoretical and practical considerations that highlight the importance of understanding nasal physiology and its effect on lower airways pathology.

We examined a number of parameters to determine a possible mechanism of this effect on conditioning. The mucosal tempera-

ture was significantly lower at baseline measurement on budesonide as compared with placebo in nonsmokers, which would be expected to reduce nasal conditioning. In the lungs, the vasoconstrictor effect of topical steroids is short-lived (17); therefore, we would not expect the morning dose to affect the measurements of nasal conditioning capacity hours later in each subject. Additionally, studies of intranasal budesonide have not shown a significant vasoconstrictor effect (18–19). Treatment with budesonide can reduce the mucosal temperature by decreasing blood flow induced by inflammation. A reduction of nasal mucosal temperature would be predicted to reduce nasal humidification and thus explain our observation.

Nasal volumes were not significantly different between treatments at baseline measurement on either treatment, although a trend for larger volume was seen with budesonide, consistent

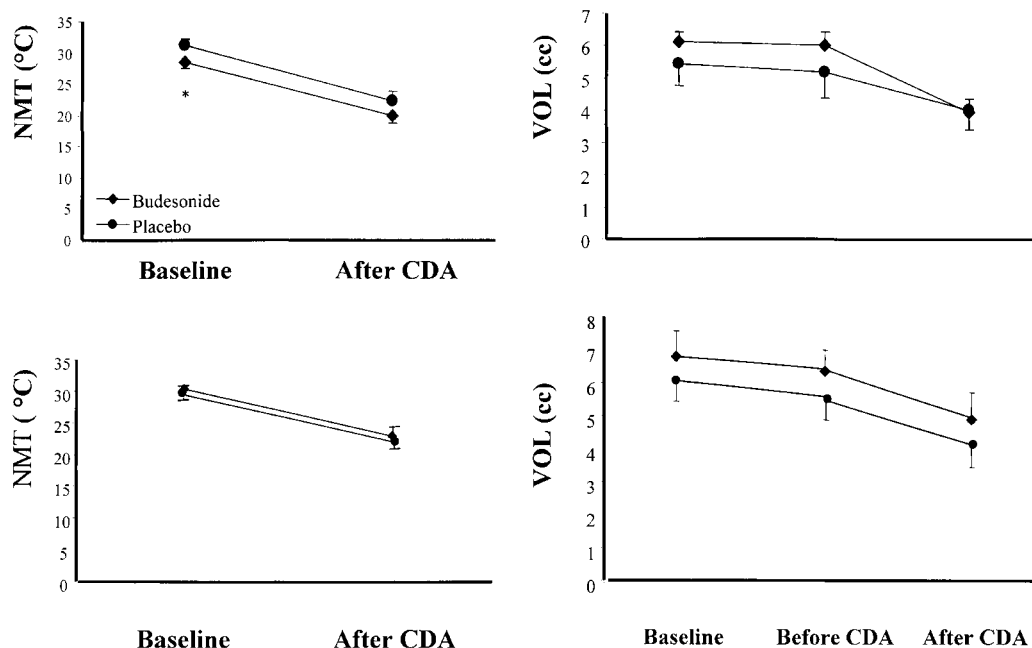


Figure 4. Nasal cavity temperature and volume. *Top left panel:* Nasal mucosal temperature, with time points on the abscissa. Data are mean $\pm$ SEM for 11 subjects. * $p < 0.05$. *Bottom left panel:* Nasal mucosal temperature in 9 smokers. *Top right panel:* Nasal cavity volume, with time point on the abscissa. Data are mean $\pm$ SEM for 11 nonsmokers. *Bottom right panel:* Data for volume in 9 smokers. Temperature was lower on budesonide in nonsmokers, but no different in smokers. Remaining changes show no significant differences. *Diamonds* = budesonide, *circles* = placebo.

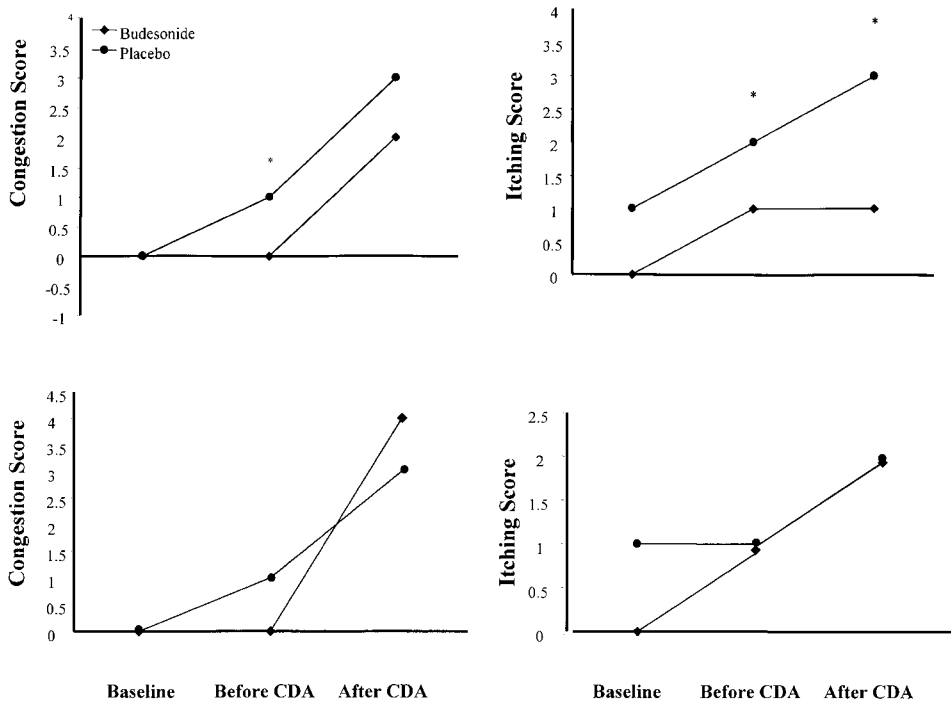


Figure 5. Symptom scores in nonsmokers. *Top right panel:* Pruritus (itching) scores, with time point on the abscissa. Medians are shown in 11 nonsmoking subjects. * $p < 0.05$. *Bottom right panel:* Data from 9 smoking subjects. *Top left panel:* Congestion scores, with time point on the abscissa. Medians are shown in 11 non-smoking subjects. *Bottom left panel:* Data in 9 smokers. *Diamonds = budesonide, circles = placebo.*

with the antiinflammatory effects of this medication. As in our previous studies, CDA caused a significant reduction in nasal volume in both treatments, which was not different. Congestion scores paralleled the decrease in nasal volume after CDA and did not vary significantly between treatments. Our prior finding that reduction in nasal volume through supine positioning worsens nasal conditioning suggests that an increase in nasal volume caused by budesonide would improve conditioning (20), the op-

posite of what we observed. Secretion weights, with parallel increases in symptoms scores of rhinorrhea, were elevated after treatment with both placebo and budesonide, making this an unlikely mechanism (2–4). Our examination of cell or eosinophil counts in nasal lavage did not show a difference between treatments in either group. The lack of significant changes in these numbers reflects a minimal amount of surface inflammation occurring in the nasal passages of our subject population, making it difficult to detect a difference. Albumin levels, however, were significantly lower on budesonide compared with placebo in nonsmokers, suggesting that vascular permeability was positively affected by budesonide. Our finding is consistent with the report of budesonide decreasing vascular permeability in a study of seasonal allergic rhinitis (21). The decrease in albumin probably results from an indirect effect on the permeability of the nasal vasculature through inhibition of inflammation, with its resultant release of mediators that increase vascular leakage (22). It is interesting that this effect was not seen in smokers, suggesting that smoking causes an opposing effect or mitigates the effect of budesonide on this phenomenon. Additionally, the inflammation in smokers with asthma may be different than that in nonsmokers, as evidenced by the finding by Chalmers and coworkers, who found smoking is associated with neutrophilic airway inflammation and elevated interleukin-8 production in individuals with asthma (23).

Other factors that may account for the effect of an intranasal steroid on conditioning are the nasal mucosal area, the thickness of the mucosa-submucosa and mucous layer, and ion transport (24–27). A 2-week treatment with intranasal steroid is unlikely to affect structural changes in the nasal mucosa, but an effect on ion transport cannot be excluded.

There are limited data on the effect of topical steroids on ion/water transport in upper-airway epithelia in humans. Steroids have been shown to increase sodium absorption across epithelial cells *in vivo* and *in vitro*, which would theoretically cause increased absorption across of airway surface fluid, decreasing nasal conditioning, and therefore might explain our

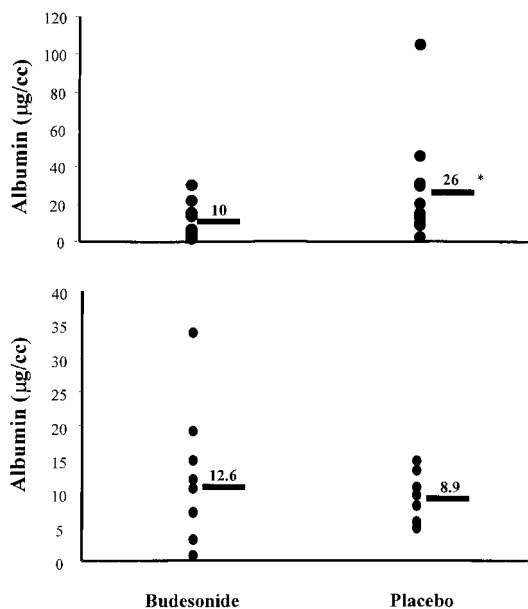


Figure 6. Albumin levels in nasal lavage. Individual data are shown with treatment on the abscissa. The solid bars with the number above represent the means of individual data points. * $p < 0.05$. Nonsmokers are seen above, smokers below.

findings with budesonide (28–30). In contrast, inflammatory pathways can increase the secretory response in allergic rhinitis and asthma. For example, interleukin-13 can convert human bronchial epithelium *in vitro* from an absorptive to hypersecretory state (31). This could explain our previous finding that allergic inflammation enhances nasal conditioning (3). It also could explain the results of this study by downregulating inflammation; budesonide might decrease the effects of these mediators on increasing conditioning.

Perhaps our most intriguing finding is that cigarette smoke can affect the response to intranasal steroids. This is important clinically because up to 35% of individuals with asthma continue to smoke. The detrimental effects of cigarette smoke on both the upper and lower airways are well known, and a number of investigators have examined how smoking affects water transport. Smoking can cause disruption of active sodium transport (32). Nicotine can cause intracellular calcium release that may regulate ion transport (33). Mean epithelial lining fluid in smokers was greater than that of nonsmokers, either from increased production of fluid or impaired clearance (34). Most studies show that smoking increases vascular permeability in the lower airways (35–36). Cigarette smoke is also known to inhibit mucociliary clearance, increase recruitment of inflammatory cells, and stimulate nasal epithelial hyperplasia; any of these reactions could affect nasal conditioning (33). The lack of difference in physiologic parameters such as temperature, volume, secretion weight, eosinophil count, or albumin level at baseline on placebo (Table 2) argues that these measures could not explain our results.

The effect of smoking on the nasal conditioning capacity may also be mediated by inflammation (37–38). Smoking may enhance nasal conditioning by inducing inflammation that is resistant to the effects of intranasal steroids. Indeed, the lack of effect of budesonide on albumin levels seen in smokers suggests such relationship may be present. A recent randomized, placebo-controlled study by Thomson and colleagues showed that active cigarette smoking in individuals with asthma was associated with resistance to short-term, high-dose corticosteroids, a finding consistent with our observations (39). The mechanism for this effect is unknown, but may be due to the immunologic effects of cigarette smoke (40–43). A variety of other mechanisms have been proposed.

In conclusion, our data demonstrate that budesonide decreases the ability of the nose to warm and humidify air in nonsmoking subjects with asthma. The mechanism of this effect probably involves an effect on decreasing inflammation, which actually improves nasal conditioning. The effects of cigarette smoking highlight the clinical and physiologic importance of understanding nasal function. These results demonstrate the complex physiology of the nose and its responses to a common pharmacologic intervention. Further investigations will be required to dissect the complex molecular mechanisms of this physiologic process. Such studies are likely to provide insights into the complex relationship of inflammation, epithelial function, and water transport, insights that may lead to improved clinical therapies for human airway disease.

Conflict of Interest Statement: J.M.P. does not have a financial relationship with a commercial entity that has an interest in the subject matter of this manuscript; P.A. does not have a financial relationship with a commercial entity that has an interest in the subject matter of this manuscript; F.M.B. has received honoraria for lectures by Merck Inc. and GSK in the amount of \$10,000/year and \$3,000/year, respectively, and has also received a medical school grant from Merck Co. in 2003–2004 in the amount of \$40,000; E.N. does not have a financial relationship with a commercial entity that has an interest in the subject matter of this manuscript; J.S. does not have a financial relationship with a commercial entity that has an interest in the subject matter of this manuscript; R.M.N. has received a grant for this study from AstraZeneca.

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