

Nasal cytology in patients with allergic rhinitis: Effects of intranasal fluticasone propionate

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Background: Nasal cytograms of patients with allergic rhinitis contain increased numbers of eosinophils and basophilic cells. Neutrophils are also more numerous in cytograms of allergic persons. Topical intranasal corticosteroid therapy for allergic rhinitis has been shown to decrease the numbers of some inflammatory cell types. Fluticasone propionate aqueous nasal spray, a potent synthetic corticosteroid preparation, is effective therapy for seasonal and perennial allergic rhinitis.

Methods: Nasal mucosal scrapings were obtained with a Rhinoprobe (Apotex Scientific, Inc. Arlington, Texas) before and after therapy with fluticasone propionate aqueous nasal spray at several doses in patients with either seasonal allergic rhinitis (2 to 4 weeks' therapy) or perennial allergic rhinitis (24 weeks' therapy). More than 1000 paired nasal cytograms obtained from patients participating in five multicenter studies were evaluated.

Results: The percentage of patients with nasal eosinophils ($p < 0.01$, most studies) and basophilic cells ($p < 0.05$, most studies) decreased significantly after treatment with fluticasone propionate compared with placebo-treated patients. Similar findings were observed with beclomethasone dipropionate in one study. The number of neutrophils remained relatively unchanged after treatment with the intranasal corticosteroids or placebo.

Conclusions: These findings suggest that the therapeutic benefits of topical intranasal fluticasone propionate and beclomethasone dipropionate for the therapy of seasonal and perennial allergic rhinitis are reflected by the decrease in inflammatory cells in the nasal mucosa. (*J ALLERGY CLIN IMMUNOL* 1994;94:708-15.)

Key words: Allergic rhinitis, intranasal corticosteroids, fluticasone propionate, nasal cytology

The allergic response is biphasic whether studied in the nose, lungs, or skin. The early phase reaction occurs within 30 minutes after natural allergen exposure or challenge and may be followed by the late-phase reaction 3 to 11 hours later in some patients. The early phase reaction in the nose is characterized by the classic symptoms of sneezing, itching, congestion, and rhinorrhea. In allergen challenge studies, increased numbers of eosin-

Abbreviations used

SAR: Seasonal allergic rhinitis
PAR: Perennial allergic rhinitis

ophils are found in nasal secretions and histamine and many other mediators are detected in nasal washings.^{1,2} Symptoms and mediators may decrease (quiescent phase); however, in many patients both symptoms and mediators may subsequently increase spontaneously.³ This late-phase reaction is also characterized by a large influx of inflammatory cells, including eosinophils, basophilic cells, neutrophils, lymphocytes, and macrophages, as observed in nasal biopsy specimens.⁴

Nasal mucosal samples of allergic subjects symptomatic with allergic rhinitis also show increased numbers of eosinophils, basophilic cells, neutrophils, and goblet cells in specimens obtained by mucosal scraping.^{5,6} Eosinophils are the dominant feature of allergic rhinitis and are found

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in nasal secretions and in the airway tissues. Significant increase in nasal secretion eosinophilia occurs within 30 minutes after a positive nasal allergen challenge.^{1,7} Under natural conditions, eosinophils are detected in allergic patients only during exposure to allergen.⁸ In university students, school children, and infants, a highly significant correlation has been shown with nasal secretion eosinophilia and evidence of allergic symptoms and signs, such as nose rubbing, sneezing, sniffing, runny nose, and wet and swollen turbinates.^{9,10} The accumulation of eosinophils and eosinophil products (e.g., major basic protein, eosinophil cationic protein) have been observed during allergen-induced late-phase reactions,¹¹ and they are cytotoxic to the respiratory epithelium.¹²

Basophils are also increased in the nose in allergic disease. The normal basophilic cell content of the nose is about 200 to 400 cells/mm³ of mucosa.¹³ Basophil leukocytes constitute the majority of the basophilic cells in mucosal scrapings and in the nasal secretions.^{14,15} There is a significant correlation between their number and the level of mediators such as histamine.^{16,17} The number of basophilic cells frequently increases after 4 to 5 days of natural pollen exposure and decreases in the nasal secretions during the off-season in patients with pollinosis.¹⁸ They also decrease after successful immunotherapy. The number of basophilic cells correlates with nasal eosinophils in allergic rhinitis.¹⁹ The finding of these cells or eosinophils increases the sensitivity of the nasal cytology test for confirming an allergic diagnosis to nearly 80%.²⁰

A significant number of neutrophils have also been demonstrated in the nasal secretions in allergic disease. They were noted in blown specimens in over two-thirds of the patients with allergic rhinitis.⁷ They are also recruited during late-phase reactions. Neutrophils have the potential for producing considerable airway damage by virtue of their capacity to generate potent lipid mediators, such as prostaglandins, thromboxanes, leukotriene B₄, and PAF-acether.²¹

The effectiveness of topical intranasal corticosteroid preparations for decreasing the symptoms of seasonal and perennial allergic rhinitis has been well documented.^{6,17,22-26} In addition, study of nasal lavage fluids when topical intranasal corticosteroids are administered before allergen challenge shows inhibition of the release of the mediators of both the early and the late-phase reactions and the influx of basophilic cells that

occurs on nasal antigen challenge. Recruitment and activation of eosinophils and neutrophils is also inhibited, and this may decrease some of the subsequent steps of the inflammatory process.^{17,27,28} However, the effects of topical intranasal corticosteroids on the cells in nasal mucosal scrapings have been reported in studies in which the primary emphasis has been on efficacy. Often, only some of the cell types thought to be relevant to nasal disease are mentioned.

In this context we present the effects of therapy with intranasal fluticasone propionate on the cells of nasal mucosal scrapings in large numbers of patients symptomatic with seasonal allergic rhinitis (SAR, 14- to 28-day studies) and with perennial allergic rhinitis (PAR, 24-week studies). Fluticasone propionate is a glucocorticosteroid with high topical potency,²⁹ low systemic availability,³⁰ and has demonstrated efficacy for therapy of allergic rhinitis.³¹⁻³⁷

METHODS

Patients

For the three SAR studies, adult patients were eligible to participate if they had documented symptoms of moderate to severe SAR, a history of SAR for at least 2 years, and positive skin test results to at least one prevalent seasonal pollen allergen. For the two PAR studies, adult and adolescent patients were eligible if they had moderate to severe symptoms, a history of PAR for at least 2 years, and positive skin test results to at least one perennial allergen. All patients in the PAR studies were also required to have nasal eosinophilia documented by nasal cytologic study to qualify for participation. All studies were approved by appropriate institutional review boards, and all patients gave signed, informed consent.

Study design

All five studies were multicenter double blind, parallel group, randomized, and placebo controlled.³¹⁻³⁵ One dose-ranging study compared four dosages of intranasal fluticasone propionate,³¹ three studies compared once- and twice-daily administration of intra-nasal fluticasone propionate,³²⁻³⁴ and one study compared once- and twice-daily administration of intranasal fluticasone propionate with twice-daily administration of beclomethasone dipropionate aqueous nasal spray.³⁵ The duration of treatment was 2 or 4 weeks for the three SAR studies and 24 weeks for the two PAR studies. The treatment protocols are presented in Table I.

Nasal cytology evaluation

Nasal mucosal samples were obtained before treatment and on the final day of treatment (i.e., after 2 or 4 weeks in the SAR studies and after 24 weeks in the

TABLE I. Treatment protocols

Disease	Patients (n)	Treatment/dosage	Duration
SAR ³¹	423	FP 25 µg b.i.d. FP 100 µg b.i.d. FP 400 µg b.i.d. Placebo b.i.d.	2 weeks
SAR ³²	227	FP 100 µg b.i.d. FP 200 µg q.d. Placebo b.i.d.	2 weeks
SAR ³³	301	FP 100 µg b.i.d. FP 200 µg q.d. Placebo b.i.d.	4 weeks
PAR ³⁴	365	FP 100 µg b.i.d. FP 200 µg q.d. Placebo b.i.d.	24 weeks
PAR ³⁵	466	FP 100 µg b.i.d. FP 200 µg q.d. BDP 168 µg b.i.d. Placebo b.i.d.	24 weeks

PAR studies). The nasal mucosal sample was collected under direct vision after the patient cleared the nose of excess secretions. The cupped tip of a disposable probe (Rhinoprobe; Apotex Scientific Inc., Arlington, Texas) was gently passed on the mucosal surface of the medial aspect of the inferior turbinate. Two or three short scrapes of the epithelial membrane were made to obtain the sample. The specimen was spread onto a plain slide and immediately fixed for at least 1 minute in 95% ethyl alcohol. After the excess alcohol was drained, the slide was dipped sequentially in Wright-Giemsa stain (Volu-Sol, Logos Scientific, Inc., Henderson, Nev.) for 15 seconds, in Volu-Sol buffer for 30 seconds, and in Volu-Sol hematology rinse for 5 seconds. The slide was drained of excess fluid between procedures. After air drying, the cytogram was examined under oil immersion by light microscopy. The grading was semiquantitative on a scale of 0 to 4+, as presented in Table II.⁵ Cytograms within each study were examined by one microscopist.

Statistical methods

Paired nasal cytograms (obtained before and after treatment) were analyzed. The Cochran-Mantel-Haenszel test, adjusting for investigator, was used for analysis of change in percent of patients with each cell type within each treatment and differences in cell score between treatment groups within each study. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Only patients with evaluable paired pretreatment and posttreatment nasal mucosal specimens were included in the analyses. In the three SAR

studies, 497 of 951 (52%) patients had evaluable pretreatment and posttreatment specimens. In the two PAR studies, 504 of 831 (61%) patients had evaluable pretreatment and posttreatment specimens. The percentages of patients with eosinophils, basophilic cells, and neutrophils at the start and end of treatment for each study are presented in Table III.

Eosinophils were present in 64% to 86% of patients enrolled in SAR studies. Nasal eosinophilia was required for enrollment in the PAR studies. In all five studies the percentage of patients with nasal eosinophilia significantly decreased in groups receiving fluticasone propionate or beclomethasone dipropionate, compared with patients receiving placebo.

Basophilic cells were present in 29% to 57% of patients with SAR or PAR at baseline. The percentage of patients with basophilic cells was significantly decreased in most patients receiving fluticasone propionate and in the patients receiving beclomethasone dipropionate, compared with patients receiving placebo.

Neutrophils were present in 60% to 80% of patients enrolled in the SAR studies and in 90% to 94% of patients enrolled in the PAR studies. Fewer patients had neutrophils after treatment with fluticasone propionate or beclomethasone dipropionate, but the differences from baseline were statistically significant in only two groups of SAR patients receiving fluticasone propionate 100 µg twice daily. Approximately 30% of patients had bacteria noted in their nasal mucosal speci-

TABLE II. Grading nasal cytograms

Quantitative scoring		Semiquantitative scoring	Grade
Eosinophils,* neutrophils*			
0.1-1.0	None		0
1.1-5.0	Few scattered cells		1+
6.0-15.0	Moderate number of cells and small clumps		2+
16.0-20.0	Large clumps of cells that do not cover the entire field		3+
> 20.0	Large clumps of cells cover the entire field		4+
Basophilic cells*			
0.1-0.3	None		0
0.4-1.0	Few scattered cells		1+
1.1-3.0	Moderate number of cells and small clumps		2+
3.1-6.0	Large clumps of cells that do not cover the entire field		3+
> 6.0	Larger clumps of cells cover the entire field		4+
Goblet cells†			
0%-24%	None or a few cells		1+
25%-49%	Moderate number		2+
50%-74%	Large number		3+
75%-100%	Large number, may cover entire field		4+
Bacteria			
N/A	None		0
N/A	Occasional		1+
N/A	Moderate number		2+
N/A	Large number		3+
N/A	Large number covers the entire field		4+

*Mean of cells per 10 high-power fields ($\times 1000$).

†Ratio of goblet cells to epithelial cells, expressed as percent.

TABLE III. Percent of patients with each cell type at the start and end of each study with each active treatment or placebo

Disease	Treatment	Duration (weeks)	n ⁺	Eosinophils		Basophilic cells		Neutrophils	
				Start	End	Start	End	Start	End
SAR ³¹	FP 25 μ g b.i.d.	2	55	76	44†	51	29	60	62
	FP 100 μ g b.i.d.	2	49	84	33†	51	18†	63	51*
	FP 400 μ g b.i.d.	2	50	86	34†	38	8†	74	60
	Placebo	2	56	80	84	29	41	61	73
SAR ³²	FP 100 μ g b.i.d.	2	41	83	32†	49	10	71	63
	FP 200 μ g q.d.	2	51	76	43*	39	31	80	67
	Placebo	2	42	64	69	45	26	69	64
SAR ³³	FP 100 μ g b.i.d.	4	51	78	51†	57	31	75	63*
	FP 200 μ g q.d.	4	51	78	43†	47	31	76	76
	Placebo	4	51	69	76	37	45	71	82
PAR ³⁴	FP 100 μ g b.i.d.	24	77	100	32†	53	5†	92	78
	FP 200 μ g q.d.	24	84	100	32†	57	7*	92	80
	Placebo	24	78	100	58	52	18	90	83
PAR ³⁵	FP 100 μ g b.i.d.	24	73	100	53*	55	21†	92	88
	FP 200 μ g q.d.	24	75	100	59*	55	15†	92	84
	BDP 168 μ g b.i.d.	24	53	100	32†	57	17†	94	81
	Placebo	24	64	100	77	50	53	92	92

n⁺, Number of paired evaluable samples.

Within study p values.

*p < 0.05 vs placebo.

†p < 0.01 vs placebo.

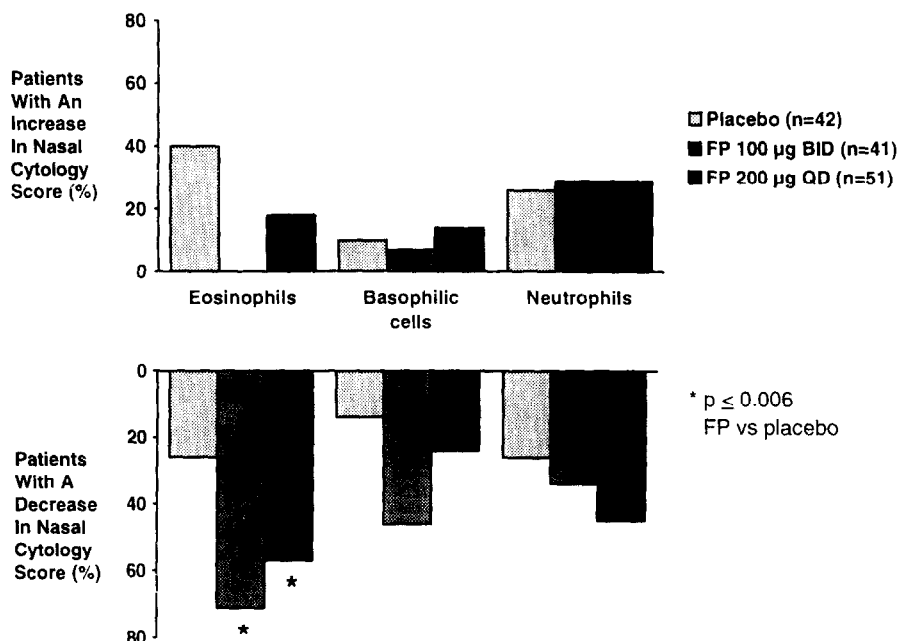


FIG. 1. Percent of SAR patients with an increase or decrease in eosinophils, basophilic cells, and neutrophils at the end of each treatment (2 weeks) by comparison with pretreatment. (*P* values are for differences between each active treatment and placebo.)

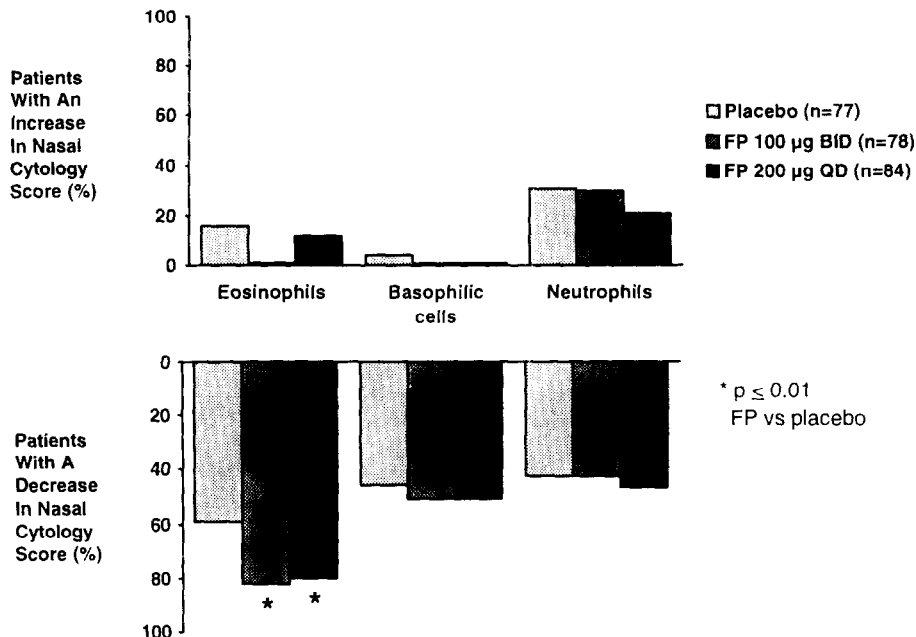


FIG. 2. Percent of PAR patients with an increase or decrease in eosinophils, basophilic cells, and neutrophils at the end of each treatment (24 weeks) by comparison with pretreatment. (*P* values are for differences between each active treatment and placebo.)

mens at baseline. There was no significant change in this percentage after any of the treatment regimens. All patients had similar numbers of goblet cells before and after treatment.

In addition to statistical analysis of percentage of patients who had each cell type present at the start and end of the treatment period (Table III), the number of patients who had an increase or

decrease in the score for each cell type was also analyzed. Within each study, significantly more patients receiving active treatment demonstrated a decrease in the score for eosinophils and basophilic cells than did placebo patients; this effect on the score for neutrophils was observed in only one SAR study.³¹ The results of one 2-week SAR study and one 24-week PAR study showing the percentage of patients with an increase or a decrease in eosinophils, basophilic cells, and neutrophils after treatment with either two dosages of fluticasone propionate aqueous nasal spray or placebo are depicted in Figs. 1 and 2, respectively.^{32, 34} Within each of these studies, significantly more patients receiving active treatment demonstrated a decrease in the score for eosinophils compared with patients receiving placebo. There were no significant changes in basophilic cells or neutrophils.

An overall summary of the data for eosinophils, basophilic cells, and neutrophils, with all treatments in which the three SAR studies are combined and the two PAR studies are combined, is illustrated in Fig. 3.

DISCUSSION

In the present study, evaluable pretreatment and posttreatment nasal mucosal samples were obtained from 1002 patients with SAR or PAR. The cytograms confirm previous reports that eosinophils are increased in patients with allergic rhinitis.^{5-10, 18} In the SAR studies approximately 80% of patients had eosinophils present before treatment. In the PAR studies 100% of patients had eosinophils present, since this was a prerequisite for participation. In all five studies the percentage of patients with eosinophils decreased after treatment with intranasal fluticasone propionate or beclomethasone dipropionate compared with patients treated with placebo ($p < 0.05$).

Basophils are also increased in allergic disease, although the frequency with which they are detected depends on both the method of obtaining the nasal mucosal specimen (i.e., blowing, nasal washings, nasal scraping, or biopsy) and the method of processing the sample. In a previous study using the Rhinoprobe technique, histochemical differentiation of metachromatic cells documented that the predominant metachromatic cell in allergic rhinitis was the basophilic cell and that only 6% of cells were mast cells.¹⁴ Nasal secretions obtained by blowing have few basophilic cells, compared with nasal mucosal specimens obtained by scraping.³⁸ In the studies reported here, basophilic cells were present in ap-

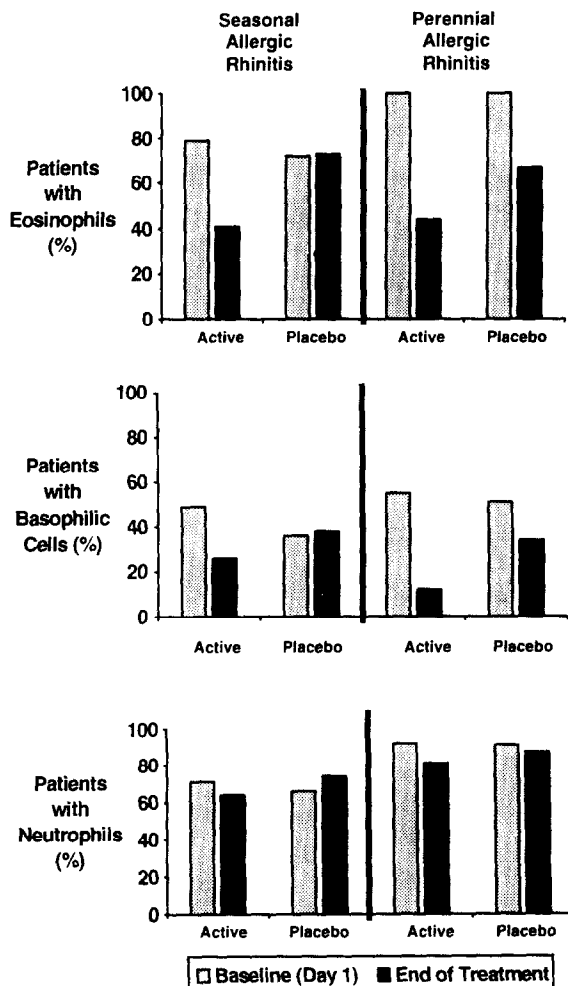


FIG. 3. Mean percent of patients with each cell type receiving fluticasone propionate or beclomethasone dipropionate or placebo in three seasonal allergic rhinitis and two perennial allergic rhinitis studies at start and end of treatment.

proximately 50% of nasal mucosal specimens before treatment. The percentage of patients with basophilic cells was significantly decreased in nearly all of the active treatment groups, compared with placebo-treated patients.

Of the cells present in the allergic nose, eosinophils and basophilic cells have received the most attention. However, neutrophils are also increased in the nasal mucosa of patients with allergic rhinitis, providing additional support for the view that allergic rhinitis is an inflammatory disease. In patients with SAR neutrophils were present in approximately 70% of pretreatment samples; in patients with PAR neutrophils were present in at least 90% of patients. The percentage of patients with neutrophils was decreased after treatment with intranasal corticosteroid

preparations but the decrease was statistically significant in only 2 of 12 active treatment groups. Similar percentages of patients had bacteria present before and after treatment. There was no evidence in these studies that use of intranasal corticosteroid preparations predisposes patients toward infection.

The symptoms of both SAR and PAR were well controlled in each of these studies in patients receiving topical glucocorticosteroid therapy, irrespective of the dose or treatment schedule, by comparison with placebo.³¹⁻³⁵ In patients with PAR, symptom control was maintained for the 6-month duration of therapy. The clinical efficacy of topical intranasal fluticasone propionate and beclomethasone dipropionate is consistent with, and may be a consequence of, the decreased numbers of eosinophils and basophilic cells that are observed in the nasal cytograms of treated patients. However, it is more difficult to explain the continued presence of neutrophils in the cytograms of patients who are symptom-free as long as they continue topical glucocorticosteroid therapy. A lack of concordance between skin test results, allergy symptoms, mediators, and cell types in nasal antigen challenge studies suggests that additional, as yet unknown, factors may be involved in the allergic reaction in the nose.³⁹

As well as being helpful for diagnosis, nasal mucosal samples before and during treatment can provide objective evidence both of compliance with a treatment regimen and of its efficacy. This may be valuable with respect to antibiotic therapy for bacterial nasopharyngitis and for topical glucocorticosteroid therapy for allergic disease.

Evaluation of nasal cytology provides objective criteria for differentiation between allergic, non-allergic and infectious rhinitis. However, in the nonallergic rhinitis with eosinophilia syndrome, nasal cytology must be considered together with other data, such as skin test results. In this syndrome only nasal secretions obtained by blowing have been studied; there are no reports of the cell types evaluated in nasal scrapings.⁴⁰ The Rhino-probe method of obtaining nasal mucosal samples is minimally invasive and may be used when it is not possible to obtain a blown secretion, for example, in children. In addition, more cell types are present than in blown samples.³⁸ The technique is easy to learn, and the results are reproducible.

Symptoms of allergic rhinitis are associated with the influx of inflammatory cells in the nasal mucosa, including eosinophils, basophilic cells,

and neutrophils. These studies show that fluticasone propionate aqueous nasal spray and, in one study beclomethasone dipropionate aqueous nasal spray, decrease the number of eosinophils and basophilic cells in the nasal mucosa of patients with seasonal or perennial allergic rhinitis. These findings suggest that the therapeutic benefits of topical fluticasone propionate and beclomethasone dipropionate are related to the decrease in these inflammatory cells in the nasal mucosa.

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