

Efficacy and onset of action of fluticasone propionate aqueous nasal spray on nasal symptoms, eosinophil count, and mediator release after nasal allergen challenge in patients with seasonal allergic rhinitis

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**D. Wang¹, F. Duyck², J. Smits³,
P. Clement¹**

Departments of ¹Otorhinolaryngology and
³Radioimmunology, University Hospital, Free
University of Brussels (VUB), Brussels;

²Medical Department, GlaxoWellcome, Belgium

We studied the effect and onset of action of fluticasone propionate aqueous nasal spray (FPANS) on mediator release and eosinophil accumulation in nasal secretions and on nasal symptoms of patients with seasonal allergic rhinitis after nasal allergen challenge (NAC). At the end of the pollen season, 28 patients were randomized in a double-blind and crossover design to receive 7 days' treatment with FPANS (200 µg, once daily) and matching placebo. NACs were performed before and at 6 h and 1, 2, 3, and 7 days during treatment with FPANS or placebo. Nasal secretions were collected for a quantitative determination of mediators and eosinophil count before and 5 min after each challenge. Nasal symptoms were assessed by scales grading the severity of symptoms at the same time. Results showed that for mediator concentrations there was a significant decrease of leukotriene C₄ ($P < 0.001$) at 7 days after the first administration of FPANS as compared to placebo. Two days after FPANS, both eosinophil counts and eosinophil cationic protein (ECP) concentrations were lower than those of placebo (eosinophils: $P = 0.032$; ECP: $P = 0.038$). The onset became even more important at day 7 (eosinophils: $P = 0.001$; ECP: $P = 0.009$) during the FPANS treatment period. For the subjective nasal symptoms, a significant reduction of symptom scores for nasal obstruction occurred also at day 3 ($P = 0.017$) and for sneezing at day 7 ($P = 0.003$). There was not yet any significant improvement of the objective nasal airway resistance after the different NACs during the study period. In conclusion, this study demonstrated that topical fluticasone propionate is effective in the treatment of mucosal inflammation induced by NAC. For optimal control of nasal symptoms induced by repeated maximal allergen challenges, a treatment period of more than 1 week is required.

Key words: eosinophils; fluticasone propionate nasal spray; inflammatory mediators; nasal allergen challenge; nasal symptoms; seasonal allergic rhinitis.

Deyun Wang, MD, PhD
Department of Otolaryngology
National University of Singapore
5 Lower Kent Ridge Road
119074 Singapore
Republic of Singapore

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The efficacy of intranasal corticosteroids on the multiple steps in the inflammatory process has been reported in many studies (1–4). They decrease mediator production, reduce mediator release, decrease production of cytokines by T-helper type 2 lymphocytes, inhibit the influx of eosinophils and basophilic cells to the nasal epithelium, and decrease the number of Langerhans' cells, suggesting a reduction in antigen presentation. There is,

however, no study assessing the efficacy of these drugs on quantitative changes of mediator release and eosinophil count in nasal secretions, in parallel with the assessment of nasal symptoms in allergic patients with a duration of therapy of less than 1 week.

The understanding of both the efficacy and, in particular, the onset of action of these commonly used topical corticosteroids in the treatment of

nasal allergic inflammation and related nasal symptoms is very important. From a clinical viewpoint, it would provide a useful guideline for appropriate use of these drugs. There is, therefore, a need for studies that provide detailed information on these issues.

In a previous study, we provided quantitative data on some important mediators and on the percentage of inflammatory cells in the nasal secretions of atopic patients during different phases after nasal allergen challenge (NAC) and during natural allergen exposure (5). Especially, the micro-suction technique proved to be a useful and reliable nasal sampling method permitting quantitative analysis of important mediators such as histamine, tryptase, leukotriene C_4 (LTC_4), and eosinophil cationic protein (ECP) during the different phases of an allergic reaction. The opportunity of measuring these specific mediators quantitatively in nasal secretions during allergic reactions provided accurate data on the activity of some important inflammatory cells (i.e., mast cells, basophils, and eosinophils) and their response to the therapy (6, 7).

This study aimed to investigate the effect and onset of action of a once daily dose of 200 μ g fluticasone propionate aqueous nasal spray (FPANS) on the mechanisms of mediator release (i.e., histamine, tryptase, LTC_4 , and ECP) and eosinophil infiltration, and on nasal symptoms as compared with placebo, in atopic patients during the early- and late-phase reactions after NAC. This study was specially designed to perform NAC at the end of the pollen season in order to provoke nasal allergic reactions in asymptomatic patients who presented with a "primed" condition of their nasal mucosa. In this circumstance, the efficacy of FPANS could be evaluated in a situation more similar to that of patients with ongoing seasonal allergic rhinitis during the pollen season.

Material and methods

Patients

During the pollen season of 1995, 28 patients (18 men and 10 women) aged 19–37 years (mean age 25.7 years) were selected from the ENT outpatient clinic (University Hospital, Free University Brussels, VUB). All of them had presented with complaints of nasal obstruction, sneezing, itching, and rhinorrhea since the start of the pollen season. Their atopy to grass pollen was confirmed by medical history and skin tests. They were then asked to return at the end of the pollen season when nasal symptoms had disappeared. At this time, they had not taken any medication for at least 2 weeks, except contracep-

tives by women. The washout period was at least 30 days for any nasal, inhaled, or systemic corticosteroid. None of the patients had any nasal inflammatory condition besides allergy. The subjects gave their informed consent. This study was approved by the local ethics committees.

Study design

This study was conducted with two periods of FPANS and placebo treatments in a randomized, double-blind, placebo-controlled, crossover design. Patients attended the outpatient clinic on five occasions during each treatment period: baseline assessment (visit [V]1), V2 (6 h later), V3 (24 h later), V4 (48 h later), and V5 (1 week after the initial visit). Every patient underwent nasal challenge with a grass pollen mixture at each visit. Assessment of nasal symptom score, nasal resistance, and nasal inspiratory peak flow were performed before and 5 min after NAC, a time point which we had previously demonstrated to be suitable for evaluating the changes in objective nasal symptoms and in mediator concentrations (5, 8). Nasal secretions were collected for the determination of mediator and eosinophil count before (at V1, V4, and V5) and 5 min after each challenge. Acrivastine 8 mg (GlaxoWellcome, London, UK) was administered orally after the final assessment of each nasal provocation, and micro-suction was applied in both treatment groups to accelerate the recovery of the patients, and to balance both groups. After a washout period of 2 weeks, the patients were crossed-over to the other treatment period. Efficacy was evaluated by comparing the difference between these two groups in measurement of mediator concentrations, eosinophil count, the records of the intensity of nasal symptoms, nasal airway resistance (NAR), and inspiratory peak flow before and after NAC.

Study medication

The patients were treated with FPANS or placebo, two puffs (50 μ g per puff) in each nostril once daily. The outer packaging of both drugs was identical. Treatment started 15 min after a complete assessment of baseline NAC. During the following days, study medication was administered each morning (15 min before the NAC on days 2, 3, and 7).

NAC and sampling procedure

NAC was carried out by nasal spray, one puff (0.04 ml of allergen solution) per nostril, with a grass pollen mixture (20 000 AU/ml, HALAB Allergy Service, Brussels, Belgium) solution. The allergen

solution was routinely stored in a refrigerator and warmed up at room temperature before use.

We used Biewenga's aspiration system, as described previously (9, 10). Briefly, each sample was collected by repeated aspiration from the floor of both nasal cavities and the surface of the inferior turbinate into a preweighed plastic sampling tube. This was immediately followed by aspiration of a known volume (1.0 ml) of phosphate-buffered saline (PBS), pH 7.4, including 10% Mesna (UCB Pharmaceuticals Company, Brussels, Belgium), to rinse the suction device and dilute the viscous sample. Mesna is added to disrupt the disulfide bonds of the mucus polypeptide chains and to decrease the viscosity of the samples; this is necessary to enable the pipetting of accurate and precise volumes of nasal aspiration fluids. The total amount of secretion sampled was measured by weighing the collection tube and the tube with the aliquot of PBS before and after sampling on a balance with a precision of 10 mg. The individual dilution factor could then easily be calculated from these parameters. The samples were cooled on ice immediately after sampling, mixed on a Vortex mixer, and centrifuged at 1000 g at 4°C for 15 min. The supernatants were stored at -20°C or -80°C until measurement.

Subjective evaluation of the nasal symptoms

The four major nasal symptoms, nasal obstruction, sneezing, itching, and rhinorrhea, were recorded on scales grading the severity of symptoms: 0=none: no symptom evident; 1=mild: symptom clearly present but with minimal awareness; 2=moderate: definite awareness of symptom, which is bothersome but tolerable; 3=severe: symptom is hard to tolerate and interfering with activities of daily life/sleeping. A total nasal symptom score (sum) was calculated by adding these four scores together for each patient, and the same scales grading the severity of a total symptom score were used.

Objective evaluation of the nasal symptoms

NAR was measured by passive anterior rhinomanometry (PAR) (Bad Ems, Germany), expressed in Pa/cm³ per s of the left (R_l) and right (R_r) sides. Total nasal resistance (R_{tot}) was computed from the following equation: $R_{tot} = R_l \times R_r / (R_l + R_r)$ (11, 12). In addition, a Youtlen peak nasal inspiratory flow meter (PNIF) (Clement Clarke International Ltd, London, UK) was also used to measure total nasal air flow.

Measurement of the mediators

Histamine, tryptase, and ECP were determined by radioimmunoassay (RIA) or immunoradiometric

assay (IRMA), according to the manufacturer's instructions (RIA or IRMA kits from Pharmacia, Uppsala, Sweden), as previously described (5, 13). LTC₄ was determined by enzyme immunoassay (EIA) (EIA kits from Laboratoire des Stallergènes, Fresnes, France). After addition of the enzymatic tracer and the specific antiserum to the samples, they were incubated for 18 h at 22°C in subdued light. This was specified in the protocol in order to minimize cross-reaction with LTD₄ (46%), LTE₄ (2%), and LTB₄ (<0.1%) (5, 13). For evaluation of the possible influence of Mesna, this product was added in recovery experiments and was shown not to influence the results of these determinations.

Cellular examination

After removal of the supernatant, the cell pellets were resuspended in 1 ml PBS, pH 7.2, containing 5% bovine serum albumin (BSA). A volume of 100 µl of Mesna was added, and the tubes were incubated for 30 min at 37°C. Longer incubation times were sometimes necessary to dissolve very viscous mucus present in the secretions. The cells were washed with PBS-1% BSA, and cytocentrifuge preparations were made. They were then stained with May-Grünwald-Giemsa and examined by light microscopy. One hundred leukocytes were evaluated and a differential count was made.

Statistical evaluation

All statistical tests were carried out two-tailed at the 5% level of significance with the SAS statistical package (version 6.08), on an IBM-compatible microcomputer. This was done by independent statisticians. For none of the variables was a hypothesis formulated on the direction of the difference between the active treatment and the placebo treatments.

All evaluations used the previously described nonparametric approach for two-period crossover trials (14). Briefly, the evaluation of the inflammatory mediators and the eosinophil counts in the nasal secretions was performed separately for each sample. Furthermore, on days on which micro-suction was performed before and after the challenge, an evaluation was made of the change during the challenge. The evaluation of individual nasal symptom score, total nasal symptom score, NAR, and nasal inspiratory peak flow was based upon the change observed during the challenge, and was performed separately for each study day.

Results

All test subjects completed their tests according to this study protocol. None of the patients had

obvious symptoms of asthma or other complication requiring additional medication. The amount of secretion obtained from each patient varied between 110 and 660 mg (median: 280 mg). It was easier to obtain more secretions after NAC, because all the patients experienced rhinorrhea immediately after NAC. To maintain an equivalent dilution factor in all samples, we always tried to obtain an equal amount of nasal secretions (about 250 mg), which was close to the median value mentioned.

Subjective symptoms

At the beginning of the first period, all patients were symptom-free except for one patient who had mild symptoms of rhinorrhea and obstruction at the baseline. A significant reduction of nasal obstruction complaints at day 3 during NAC was observed in the FPANS-treated group ($P=0.017$). Additionally, there was a significant decrease of sneezing ($P=0.003$) and an almost significant decrease of itching ($P=0.059$) during NAC at the end of the treatment (day 7) (Fig. 1). A significant reduction of the changes of the total symptom score after NAC at days 3 ($P=0.007$) and 7 ($P=0.038$) was observed in the FPANS-treated group (Fig. 2).

Objective symptoms

There was no statistical difference in the changes in total NAR (NAR_{tot}) and inspiratory peak flow value between the two treatment groups after NAC. However, there was an almost significant increase of nasal inspiratory peak flow value at day 3 in the FPANS-treated group ($P=0.058$).

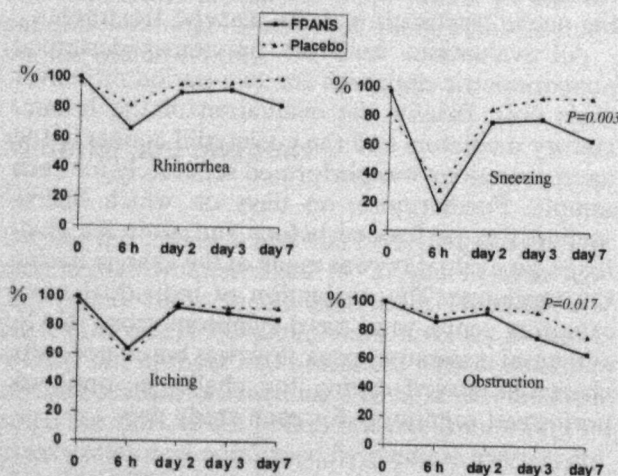


Fig. 1. Percentage of patients with moderate or severe symptom score 5 min after NAC in two treatment periods (FPANS and placebo). P values refer to change in score before and after NAC.

Mediator release after NAC

Table 1 shows the mean and median concentrations of the mediators and eosinophil count in these patients at the beginning of the study. The changes of these mediators and eosinophils after NAC at different visits are shown in Figs. 3 and 4. Fig. 3 shows that 6 h after the first administration of FPANS, NAC-induced increases of histamine and LTC_4 were significantly lower (histamine: $P=0.027$; LTC_4 : $P=0.021$) than with placebo. A significant reduction of LTC_4 concentration was also seen at the end of FPANS treatment ($P<0.001$).

Eosinophil count and ECP concentration

Fig. 4 shows the significant decrease in ECP concentration ($P=0.038$) and eosinophil count at day 3 before NAC ($P=0.032$). These differences became more significant at the end of the treatment period (ECP: $P=0.009$; eosinophil: $P=0.001$). We have previously demonstrated that ECP release does not occur during the early phase, but only during the late phase after NAC. By contrast, ECP concentration decreased in nasal secretions during the early phase because of a dilution factor caused by rhinorrhea (10).

Comparison of the changes of all measurements in the two treatment groups together after NAC between the two periods

Significantly lower histamine and tryptase concentrations after NAC, as well as a lesser increase of NAR_{tot} , were observed during the second period than the first treatment period (Table 2).

Discussion

Allergic rhinitis is an inflammatory disease of the nasal mucosa. The underlying mucosal inflammation has been characterized by the presence of basophilic cells and eosinophils in nasal smears; an epithelial accumulation of mast cells and eosinophils; and an increase in mucosal Langerhans' cells, T-cell accumulation and activation, and upregulation of the vascular endothelial expression of leukocyte adhesion molecules (15). These inflammatory changes of mediator release from mast cells, basophils, and eosinophils are evidenced in a relationship with clinical symptoms such as nasal obstruction, sneezing, itching, and rhinorrhea.

During the past 10–20 years, there has been significant progress in the pharmacotherapy of allergic rhinitis. The two most commonly used agents for the treatment of this disease are topical

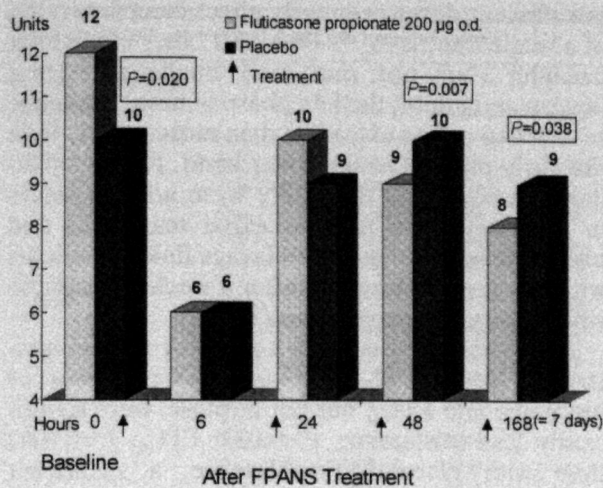


Fig. 2. Median changes of total nasal symptom score after NAC between two treatment periods.

Table 1. Median concentrations of mediators and eosinophil count in nasal secretions of all patients at baseline

Mediators	Median	Range	SD
Histamine (ng/g)	23.3	1.8–52.3	14.05
Tryptase (µU/g)	1.33	0–30.2	6.96
LTC ₄ (ng/g)	1.44	0.3–10.5	2.33
ECP (ng/g)	203	11–1383	400
Eosinophils (%)	0.50	0–40	7.79

corticosteroids and antihistamines, which have been demonstrated to be effective. In most clinical trials, the assessment of the efficacy of antiallergic drugs basically depends upon the two criteria of clinical efficacy (relief of symptoms) and reduction of the underlying inflammation. In addition, we believe that the duration of effect of these drugs after administration is also important. In particular, it is known that the beneficial effects of steroids depend upon their long-term anti-inflammatory effect rather than direct receptor antagonism. This differs from antihistamines, which block both neural and vascular H_1 -receptors and have a marked clinical effect on nasal symptoms such as itching, sneezing, and rhinorrhea. Both drugs have a marked effect on the symptoms, albeit by different mechanisms. Steroids reduce the underlying inflammation, leading to reduced response to further challenges during the season.

It was reported that the effect of FPANS on the relief of moderate to severe symptoms of seasonal allergic rhinitis can be significantly relieved within the first 12–48 h (16). H_1 antihistamines are rapidly absorbed after oral administration and begin to reduce nasal symptoms within 30 min (17).

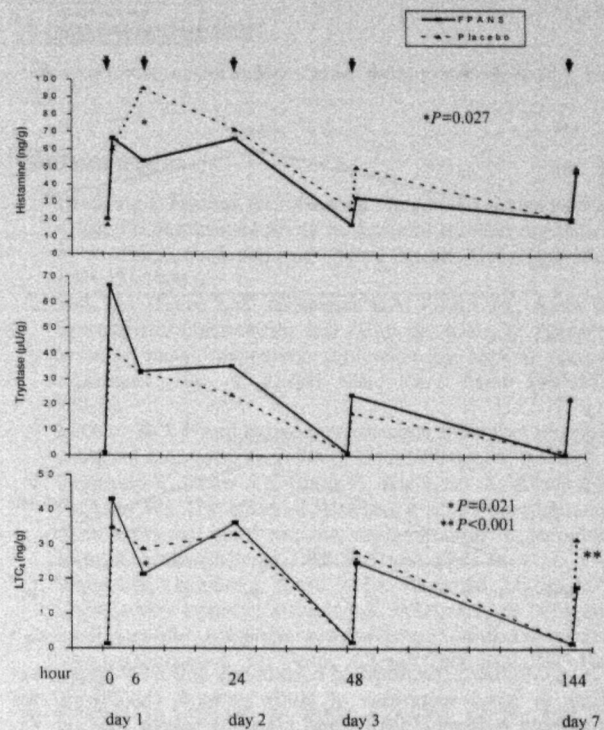


Fig. 3. Median concentrations of histamine, tryptase, and LTC₄ in nasal secretions of study patients ($n=28$) in two treatment periods (FPANS and placebo) before and after NAC at different visits. At V2 and V3, concentration of mediators was measured only after challenge.

The pharmacology of antihistamines suggests that they are less suitable for treating nasal blockage. Steroids are the only drugs which effectively treat all the symptoms of rhinitis. A better understanding of their pharmacologic properties, as well as their clinical effect (such as onset of action), is important to optimize therapy by rational use of the available drugs. Therefore, this study was designed to combine these aspects at the same time for a better assessment of the efficacy of FPANS in the treatment of allergic rhinitis.

There is evidence that corticosteroids exert their anti-inflammatory effect by inhibiting the influx of eosinophils and basophilic cells to the nasal epithelium (3, 18, 19). We have previously shown that after 2 weeks' treatment with budesonide aqueous nasal spray, there were significant reductions of the percentage of eosinophils (from a median of 44% to 1%) and ECP concentration (from a median of 633 to 60 ng/g) in patients with ongoing seasonal rhinitis during the pollen season (7). In the same patients, significant decreases of tryptase and LTC₄ concentrations, but not of histamine, were associated with a significant improvement of nasal patency (total nasal resistance and inspiratory peak flow) at 5 min after NAC with a grass pollen mixture in season. In subjective nasal symptoms,

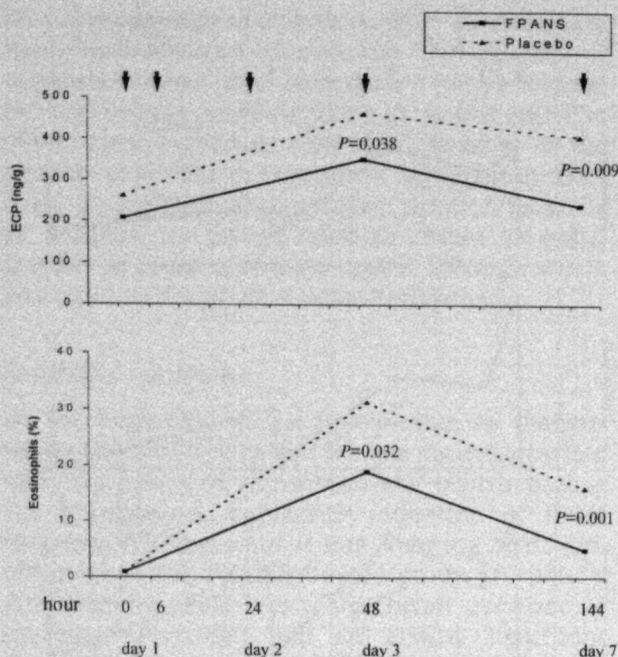


Fig. 4. Median percentage of eosinophils and ECP concentrations in nasal secretions of study patients ($n=28$) in two treatment periods (FPANS and placebo) before NAC at V1, V4, and V5.

the improvement in the budesonide-treated group was not as effective as in the azelastine- and cetirizine-treated group (6).

In this study, we demonstrated that a significant effect of FPANS on eosinophilia and ECP release started at 48 h after the first administration, as compared to placebo. These differences became more significant at the end of 1 week's treatment. In this study, nasal secretion samples were not collected before NAC at visits 2 and 3. Therefore, there was a lack of information on the changes of ECP concentration and eosinophil count earlier than 48 h after the treatment. However, the eosinophil count did not completely return to the baseline value after 1 week of treatment, indicating that a longer administration of FPANS is needed to have a maximal effect on mucosal inflammation as expressed by eosinophilia, particularly since the patients were repeatedly challenged with a maximal dose of allergen extract. Under this condition, it may be that at 7 days' treatment the maximum effect of the FPANS has not yet been reached.

The effect of corticosteroids on mediator release from activated mast cells or basophils during the early-phase reaction after NAC is still a matter of controversy. The results from individual trials are controversial, probably because of such differences in study design as dose of study drug, sampling and analysis technique, and duration of observation. From the literature, it appears that corticosteroids

in sufficient doses ordinarily effect complete relief of allergic rhinitis in 12–36 h (20). They can inhibit basophil (but not mast-cell) mediator release *in vitro* and inhibit the late phase of nasal challenge reaction to pollen extract in man more readily than the early phase. On the other hand, two independent studies found that there were no differences in the number of nasal mucosal mast cells and histamine levels in the nasal lavage fluid of patients with hay fever before and after 4 weeks' treatment with fluticasone propionate (21, 22).

This study showed that 6 h after the first administration of FPANS, NAC-induced increases of histamine and LTC_4 , but not tryptase, were significantly less (histamine: $P=0.027$; LTC_4 : $P=0.021$) than with placebo. Furthermore, a significant reduction of LTC_4 concentration was found only at the end of the FPANS treatment period. From this study, it appears that the effect of 1-week treatment with FPANS on mediator release during the early-phase reaction after NAC is not highly convincing. Correspondingly, there seemed to be a tendency to improvement in change of nasal symptoms scores during NAC, as indicated by significant (or almost significant) decreases of nasal complaints of rhinorrhea ($P=0.056$), obstruction ($P=0.0017$), total symptom score ($P=0.007$), and nasal inspiratory peak flow ($P=0.058$) at 72 h, and itching ($P=0.059$), sneezing ($P=0.003$), and total symptom scores ($P=0.038$) at the end of the FPANS treatment period. The effect of FPANS on the relief of subjective (symptom score) and objective (nasal resistance and inspiratory peak flow) nasal observations had not reached its maximal effect within 1 week. Accordingly, an atopic patient exposed to very high pollen concentrations during the season (as experienced in this challenge study) may require a fast-acting H_1 antihistamine for the quick relief of symptoms, in addition to the administration of an intranasal corticosteroid to reduce the underlying inflammation. Ideally, anti-inflammatory therapy should be instituted at the beginning of the season before the pollen burden becomes too great.

We have observed in both treatment groups that sneezing, itching, and rhinorrhea had obviously decreased during NAC only at 6 h after treatment as compared to the baseline challenge. Perhaps the residual effect of acrivastine, which was used as rescue medication in all patients after allergen challenge, may have influenced these findings at the 6-h challenge. Indeed, the antihistamine effect of this drug lasts longer than 6 h.

A period effect was observed for significantly higher histamine and tryptase concentrations during NAC at period one than period two. There was also a lesser increase of total nasal resistance at the second period. The decreased concentrations of

Table 2. Comparison of median values of measurements in whole study population (FPANS and placebo) during two treatment periods

Parameters after allergen challenge		Period 1	Period 2	P value*
Histamine	Day 1/0 h	80.85	51.95	0.002
	Day 1/6 h	78.84	74.71	NS
	Day 2	88.56	47.22	0.001
	Day 3	47.24	39.44	NS
	Day 7	53.63	43.03	0.009
Tryptase	Day 1/0 h	64.21	22.77	0.027
	Day 1/6 h	49.07	17.73	0.003
	Day 2	39.53	16.43	<0.001
	Day 3	29.78	16.78	0.021
	Day 7	24.45	20.19	0.021
LTC ₄	Day 1/0 h	43.01	35.16	NS
	Day 1/6 h	30.07	23.92	NS
	Day 2	37.91	27.18	NS
	Day 3	25.57	28.08	NS
	Day 7	27.70	29.31	NS
Total nasal symptom scores	Day 1/0 h	12.0	11.0	NS
	Day 1/6 h	7.0	8.0	NS
	Day 2	12.0	11.0	NS
	Day 3	12.0	10.0	0.003
	Day 7	11.0	9.0	0.039
Peak flow	Day 1/0 h	35.0	50.0	NS
	Day 1/6 h	0.0	45.0	NS
	Day 2	15.0	50.0	NS
	Day 3	40.0	70.0	0.005
	Day 7	55.0	65.0	NS
Total nasal resistance	Day 1/0 h	41.18	22.83	0.008
	Day 1/6 h	44.00	19.33	0.004
	Day 2	36.17	26.38	NS
	Day 3	26.43	16.33	0.001
	Day 7	25.31	13.38	NS

* During changes after nasal allergen challenge.

NS: not significant.

histamine and tryptase at the second period could be explained by a decrease of the number of mast cells, or by decreasing degranulation ability due to the effect of acrivastine, or they could be related to a longer duration (5 weeks) after the pollen season than in the first period, which was only 2 weeks after the end of the season.

In conclusion, this study has confirmed that topical fluticasone propionate is effective in the treatment of mucosal inflammation induced by NAC. The onset of this effect can be demonstrated 48 h after the initial treatment. Although a significant reduction in sneezing, nasal obstruction, and several inflammatory mediators in nasal secretions could be demonstrated 7 days after the treatment, a significant effect on the other acute nasal symptoms, objective signs induced by repeated allergen challenges, could not be demonstrated. A treatment period of more than 1 week may be required to gain complete clinical control of nasal symptoms induced by repeated maximal allergen challenges.

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