The effect of nasal steroid aqueous spray on nasal complaint scores and cellular infiltrates in the nasal mucosa of patients with nonallergic, noninfectious perennial rhinitis

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Topical corticosteroids are the therapy of choice for nonallergic, noninfectious perennial rhinitis (NANIPER). However, the efficacy of steroid therapy in NANIPER is controversial, as is its mode of action. To our surprise, of 300 patients initially diagnosed as having NANIPER, only 65 reached threshold nasal symptom scores. Patients were randomized into four different treatment regimens: placebo administered twice daily (BD) for 8 weeks, fluticasone propionate aqueous nasal spray (FPANS) (200 μg) once daily (OD) and placebo OD for 8 weeks, FPANS (200 μg) OD and placebo OD for 4 weeks followed by FPANS (200 μg) BD for 4 weeks, and FPANS (200 μg) BD for 8 weeks. A small decrease in nasal symptoms was found, which only reached significance for sneezing in the FPANS 200 μg BD group. A significant dose-dependent decrease in immunocompetent cells was found in nasal biopsy specimens obtained before, after 4 weeks, and after 8 weeks of treatment. We conclude that FPANS did not significantly reduce nasal symptoms in this group of selected NANIPER patients, even though a significant effect on cells in the nasal mucosa was seen. (J Allergy Clin Immunol 1997; 100:739-47.)

Key words: Nonallergic, noninfectious perennial rhinitis, topical steroids, fluticasone propionate, nasal biopsies, immunohistochemistry, nasal symptoms

Abbreviations used

BD:	Twice daily
DRC:	Daily record chart
FPANS:	Fluticasone propionate aqueous nasal spray
mAb:	Monoclonal antibody
NANIPER:	Nonallergic, noninfectious perennial rhinitis
OD:	Once daily
PBS:	Phosphate-buffered saline
ssAP:	Supersensitive immunoalkaline phosphatase
VAS:	Visual analog scale

Topical corticosteriods became firmly established as the therapy of choice for allergic rhinitis in the last decades. Patients with this disorder do greatly benefit from this treatment.[1, 2] The effects of local steroids in the nasal mucosa in allergic rhinitis have been well documented.[3-5] The first studies showing the efficacy of topical steroids in nonallergic, noninfectious perennial rhinitis (NANIPER) were performed in the late 1970s and the early 1980s.[6-8] Recent studies that have used fluticasone propionate aqueous nasal spray (FPANS) for the treatment of NANIPER have shown an efficacy comparable to that of topical steroids in the treatment of allergic rhinitis.[9] Philip and Togias,[10] however, stated that although some clinical efficacy has been demonstrated in the treatment of NANIPER, these agents often failed to provide the same relief as they did in the treatment of allergic rhinitis.

There are two theories concerning the etiology of NANIPER.[11] The first theory assumes an imbalance between adrenergic and cholinergic innervation of the nasal mucosa.[12] In this scenario, underactivity of the sympathetic nervous system leads to nasal obstruction, whereas overactivity of the parasympathetic nervous system leads to rhinorrhea.[13] Support for this theory was found by Wilde et al.,[14] who showed an abnormal response to isometric exercise in patients with NANIPER, possibly caused by relative nasal sympathetic hyposensitivity.

According to the second theory, NANIPER could be the result of an "overactive" nonadrenergic, noncholinergic system, resulting in neurogenic inflammation.[15, 16] Stimulation of sensory neurons results in sensory nasal changes, rhinorrhea,[17] nasal blockage, and sneezing. Sensory neural stimulation may produce these effects either through a central neural reflex associated with efferent parasympathetic neurotransmission or through antidromic release of neuropeptides from sensory neurons.[18] To support this hypothesis, Lacroix et al.[19] reported an increased concentration of neuropeptides in a

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TABLE I. Selection criteria for NANIPER

Inclusion criteria
- Age between 16 and 64 years
- Negative skin prick test response to house dust mite, tree pollen mix, grass pollen mix, bijvoet, *Alternaria, Aspergillus, Cladosporium, Penicillum,* dog, cat, parakeet, rabbit, hamster, horse, guinea pig*
- Negative Phadiatop result
- Symptoms for more than 1 year
- Periods of nasal discharge, sneezing, and congestion for an average of at least 1 hour per day for at least 5 days during a period of 14 days

Exclusion criteria
- Use of systemic or inhaled corticosteroids within the previous month
- Use of inhaled sodium cromoglycate or nedocromil sodium within the previous month
- Use of astemizole within the previous month
- Inability of the patient to stop taking medication affecting nasal function
- A serious and/or unstable disease
- Nasal surgery within the previous 6 weeks
- Nasal polyps or a history of nasal polyps
- Significant anatomic abnormalities affecting nasal function
- Nasal or paranasal sinus infection (abnormal sinus roentgenogram)
- Pregnancy or lactation
- Abnormal laboratory results for
  - Blood: Na, K, Ca, total protein, albumin, urea, creatinine, bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, γglutamyl transpeptidase, hemoglobin, red blood cell count, plasma cell volume, mean corpuscular volume, platelets, total white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, and basophils
  - Urine: blood, protein, and glucose
- Abnormal findings at physical examination

*Allergen extracts provided by ALK-Diephuis, Holland.

TABLE II. Daily record card

Symptom	Numeric score
Nasal blockage (not being able to breathe freely through the nose)	0 = Absent 1 = Between 0-1 hr per half day 2 = Between 1-2 hrs per half day 3 = More than 2 hrs per half day
Clear discharge (runny nose)	0 = Absent 1 = Between 0-1 hr per day 2 = Between 1-2 hrs per day 3 = More than 2 hrs per day
Sneezing	0 = Absent 1 = Less than 5 periods per half day 2 = Between 5 and 10 periods per half day 3 = More than 10 periods per half day
Coughing	0 = Absent 1 = Less than 5 periods per half day 2 = Between 5 and 10 periods per half day 3 = More than 10 periods per half day
Mucus production (yellow, green, or brown)	0 = Absent 1 = Present
Eye irritation	0 = Absent 1 = Present

All other medical complaints and medication taken during the day should be noted.

group of patients with chronic rhinitis. A theoretical basis (animal experimental data) in accordance with the second theory for the efficacy of steroid therapy was found when steroids were reported to upregulate neutral endopeptidase, which degrades neuropeptides[20] and inhibits neurogenic plasma extravasation.[21]

As a diagnosis made by exclusion, NANIPER probably represents a heterogeneous group of pathophysiologic conditions. To study this disorder in a second-echelon setting, we applied strict selection criteria. We excluded patients with systemic, medical, and anatomic disorders that could explain complaints of rhinorrhea, sneezing, and nasal obstruction. The remaining group was further homogenized on the basis of a daily record chart (DRC) on which patients had to reach a minimum symptom score.

When modern immunohistochemical staining methods are used, no data are available on the effect of local corticosteroid therapy on cellular infiltrates in the nasal mucosa of patients with NANIPER. We studied the effects of different treatment regimens for NANIPER on nasal complaints and cellular infiltrates.

METHODS

Patients were studied from 1988 to 1993 in the outpatient Ear, Nose, and Throat Departments of the Leyenburg Hospital in the Hague and the Dijkzigt University Hospital in Rotterdam, The Netherlands.

Patients were admitted to the study if they had a history of nasal complaints such as nasal obstruction, sneezing, and rhinorrhea for a period of over 1 year, which could not be attributed to allergic rhinitis, nasal or paranasal sinus infection, anatomic disorders affecting nasal function (e.g., septal deviation, septal perforation, synechia, or bullous medial concha), pregnancy or lactation, systemic disorders, and/or the use of medication affecting nasal function (Table I). Patients with nasal polyps were excluded. Three hundred patients with the diagnosis of NANIPER were scored twice daily for the duration of their nasal complaints for a period of 2 weeks (run-in) by using a daily record chart (Table II). In affected patients, periods of nasal discharge, sneezing, and congestion had to persist for an average of at least 1 hour per day for at least 5 days during a period of 14 days. The duration of complaints during the day was used as the prime criterion for further study. Sixty-five of the 300 patients were found to be eligible for our study and participated under conditions of informed consent (32 men and 33 women). They had a mean age of 34 years (range, 17 to 62 years). Twenty patients had never smoked, 16 were former smokers (had not smoked for more than 1 year), and 29 were current smokers. The ethnic origin of the patients was as follows: 1 Oriental, 56 white, 2 black, and 6 Asian.

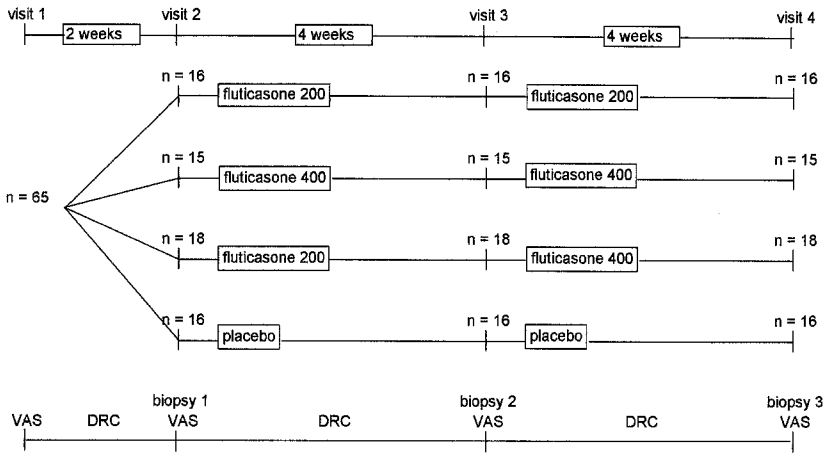

FIG. 1. Study design. *200,* FPANS 200 μg OD; *400,* FPANS 200 μg BD.

Study design

A single-investigator, multicenter, double-blind, placebo-controlled study was done. All patients started with a run-in period of 2 weeks during which they received placebo doses of aqueous spray and recorded their nasal complaints. Eligible patients were randomized into one of four different treatment regimens: placebo administered twice daily (BD) for 8 weeks, FPANS (200 μg) once daily (OD) and placebo OD for 8 weeks, FPANS (200 μg) OD and placebo OD for 4 weeks followed by FPANS (200 μg) BD for 4 weeks, and FPANS (200 μg) BD for 8 weeks (Fig. 1). The treatment period was divided into two periods of 4 weeks. Terfenadine tablets (60 μg) were used as rescue medication. The study protocol was approved by the ethical review committees and conducted in accordance with the Declaration of Helsinki.

Symptom scores

For each of the symptoms of nasal blockage, sneezing, and rhinorrhea on waking and during the rest of the day, the scores were summarized separately by the percentage of symptom-free days as done by Scadding et al.[9] The scores for coughing, mucus production, eye irritation, and number of terfenadine tablets used were recorded.

At every visit the subjects also rated the intensity of their nasal symptoms during the last 3 days on a visual analog scale (VAS) (0 to 10 cm; 0 represented absence of symptoms and 10 represented severe intensity of symptoms). This was pragmatically considered to be the golden mean for moderating the extremes in nasal symptoms per patient by scoring intensity of symptoms over several days and by having a reasonably reliable recollection period of only 3 days. At each clinic visit the investigator scored the severity of the patient's symptoms of nasal blockage, sneezing, rhinorrhea, and postnasal drip on a scale of 0 to 3 (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms). The nose was assessed by rhinoscopy. Turbinate swelling, crusting, bleeding, color of mucosa, and secretions were noted as normal or abnormal.

Safety

Safety was assessed by monitoring adverse events at each clinic visit. Biochemistry, hematology, and urinalysis results were determined at baseline and at the end of treatment.

TABLE III. Monoclonal antibodies used to study nasal mucosal biopsy specimens of patients and control subjects

Antibody	Specificity	Titer	Source
OKT6	CD1	1:100	Dept. Immunology, Erasmus University, Rotterdam, The Netherlands
Leu-4	CD3	1:25	BD, Dorset, U.K.
Leu-3	CD4	1:50	BD, Dorset, U.K
Leu-2	CD8	1:100	BD, Dorset, U.K.
α-IgE	IgE	1:250	Central laboratory of the Netherlands Red Cross Blood Transfusion Service (CLB), Amsterdam, The Netherlands
IL-2r	CD25	1:150	BD, Dorset, U.K.
BMK13	MBP	1:200	Sanbio, Uden, The Netherlands
B7	Chymase	1:100	Chemicon, Temecula, Calif
G3	Tryptase	1:250	Chemicon, Temecula, Calif

Nasal biopsies

Nasal biopsies were performed after the run-in period, after 4 weeks of treatment, and after 8 weeks of treatment in each patient (Fig. 1). After randomization of the biopsy side, specimens of the nasal mucosa were taken from the lower edge of the inferior turbinate, about 2 cm posterior to the front edge, by using a Gerritsma forceps (Entermed, Woerden, The Netherlands) with a cup diameter of 2.5 mm.[22] Local anesthesia was obtained by placing a cotton-wool carrier with 50 μg of cocaine and one drop of epinephrine (1:1000) under the inferior turbinate without touching the biopsy site. The specimens were embedded in Tissue-Tek II Optical Clear Tissue (O.C.T.; Sakura Finetek Europe BV, Zoeterwoude, The Netherlands) compound and frozen immediately.

Nasal brush cytology

After the run-in period, a nasal brush sample was taken from the middle nasal meatus contralateral to the biopsy side by using the Gynobrush (Medeco, Eindhoven, The Netherlands).

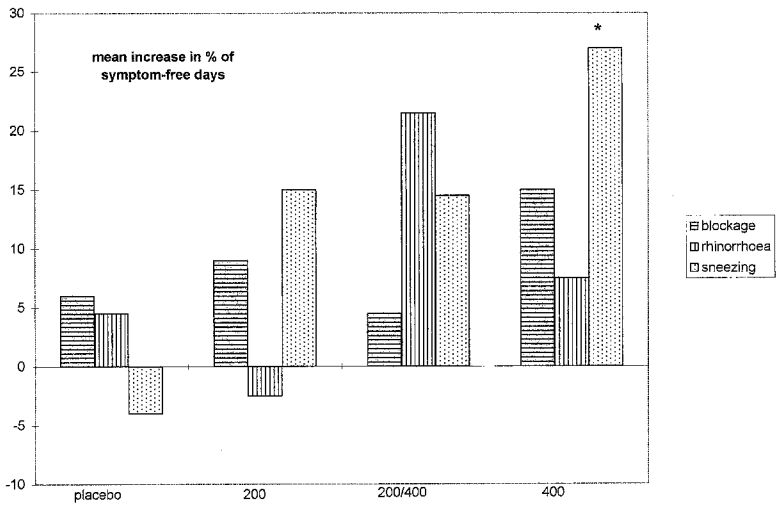

FIG. 2. Mean increase in the percentage of symptom-free days recorded on DRC during days 1 to 70. Comparison of first 14 days (between visits 1 and 2) and last 14 days (between visits 3 and 4). $*p < 0.05$ (FPANS vs placebo).

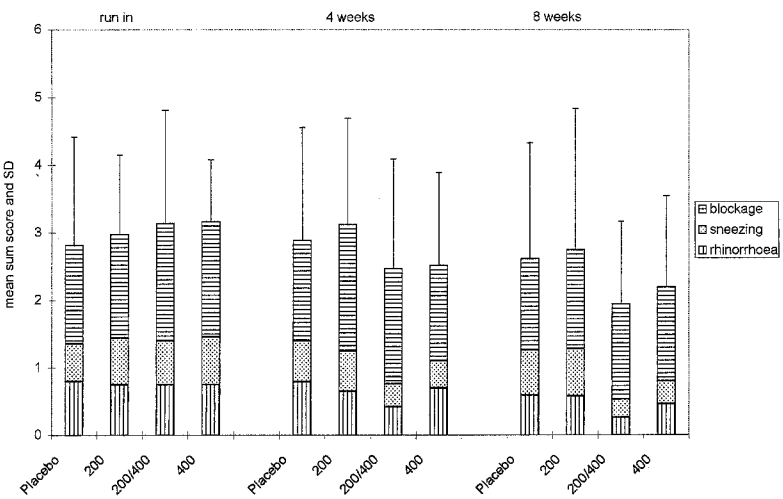

FIG. 3. Mean sum score and SD are shown for different treatment regimens in week preceding each visit.

The brush was immediately placed in RPMI 52400 (Life Technologies, Breda, The Netherlands). Within 3 days, cytospin preparations were made and cells were stained with May-Grunwald-Giemsa stain and toluidine blue.[23]

Staining procedures

Monoclonal antibodies (mAbs) directed against CD1, CD3, CD4, CD8, CD25, IgE, major basic protein, chymase, and tryptase (Table III) were used together with the supersensitive immunoalkaline phosphatase method. Sections of the nasal mucosa (6 μm) were cut on a cryostat (Jung Frigocut 2800E/20/40), transferred to poly-l-lysine–coated microscope slides, dried, and fixed in acetone for 10 minutes at room temperature. They were then rinsed in phosphate-buffered saline (PBS) (pH 7.6), placed in a half-automatic stainer (Sequenza, Shandon), incubated with 2% bovine serum albumin in PBS for 10 minutes, and incubated with normal goat serum (Central laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, The Netherlands) for 10 minutes. The slides were subsequently incubated with the mAbs for 60 minutes at room temperature. The sections were then rinsed again in PBS for 5 minutes and incubated for 30 minutes with a biotinylated goat anti-mouse (1:50) immunoglobulin antiserum (Biogenics, Klinipath, Duiven, The Netherlands), rinsed successively in PBS, incubated with streptavidin AP (1:50) (Biogenics, Klinipath) for 30 minutes at room temperature, rinsed in PBS and Tris buffer (pH 8.5), and incubated for 30 minutes with a new fuchsin substrate (Chroma, Kongen, Germany) at room temperature. Finally, sections were rinsed with distilled water, counterstained with Gills hematoxylin (Polysciences, Inc.) and mounted in glycerin-gelatin. Control staining was performed by substitution with PBS and incubation with an irrelevant mAb of the same subclass. The cytospin preparations were stained with toluidine blue (pH 0.5) for 5 minutes, and

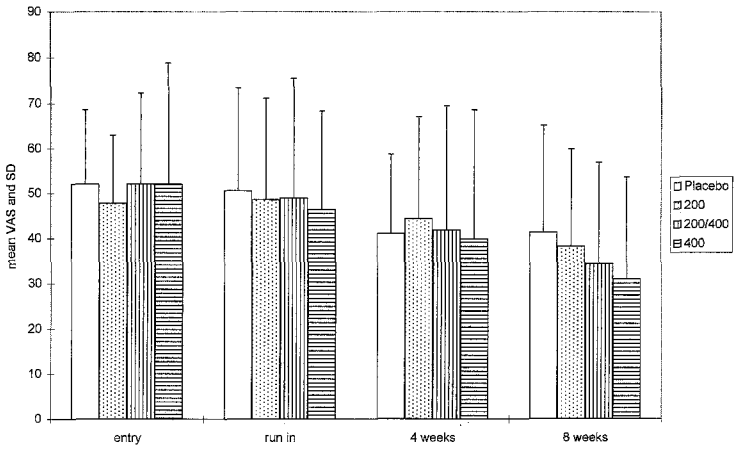

FIG. 4. Mean VAS and SD are shown as recorded during each visit.

counts were performed immediately.[24] Separate cytospin preparations were stained with May-Grunwald-Giemsa stain to study eosinophils.

Light-microscopic evaluation

Stained cells were counted in two sections of each biopsy specimen. The epithelium and lamina propria were evaluated separately. The total surface area of a section and its main parts (i.e., the epithelium and the lamina propria) were estimated with the use of the Kontron Image Analysis System Videoplan (Zeiss). The number of cells per square millimeter was calculated for the epithelium and the lamina propria.

Statistics

The mean sum scores for blockage, sneezing, and congestion were calculated during the week previous to visit 2, the week previous to visit 3, and the week previous to visit 4 because the effect of FPANS on nasal symptoms in our clinical experience reaches a steady state 1 to 2 weeks after the start of treatment. To moderate the fluctuations in DRC scores per patient, the mean sum score for 1 week was used. Statistical analysis of symptoms was carried out by testing differences from baseline among the four treatment groups (Kruskal-Wallis analysis of variance). Assessment by the investigator was analyzed with the chi-square test for trend.

The biopsy data of the FPANS 200 μg OD group and the FPANS 200 μg OD followed by BD group were pooled for biopsy number 2 because these groups received the same treatment up to that moment (the first 4 treatment weeks). The Mann-Whitney U test was used to compare the differences in cell counts between different pairs of groups after significance had been established by using the Kruskal-Wallis analysis of variance among the four treatment groups. A p value less than 0.05 was considered a significant difference.

We calculated the Spearman rank correlations between changes in cell numbers and the changes in the VAS scores per randomization group.

RESULTS

Symptom scores

Fig. 2 shows the changes in the percentage of symptom-free days during the treatment compared with baseline. A small decrease in symptoms was found, which only reached significance for sneezing. The mean increase in the percentage of symptom-free days for sneezing in the FPANS 200 μg BD group was significantly better than that in the placebo group when baseline and 8 weeks of treatment were compared (28% increase in percent points for the FPANS 200 μg BD group vs 5% decrease in percent points for the placebo group). No significant difference between the four treatment groups was seen for coughing, mucus production, eye irritation, and number of terfenadine tablets used. No significant changes were seen for the mean sums of the scores (Fig. 3) (1 week before each visit) or the VAS score (Fig. 4) among the four treatment groups. There were no statistically significant differences among the four treatment regimens in the investigators' assessments of symptoms and rhinoscopy at clinic visits.

We found no correlation greater than 0.7 absolutely, which approximately coincides with testing at an α of 0.01 between cell counts and nasal symptoms, given the size of the randomization groups.

No major adverse events occurred, and there were no relevant changes in the routine biochemical tests, hematologic tests, or urinalysis.

Nasal brushes

Five hundred cells were counted per cytospin. Toluidine blue–positive cells were found in just one cytospin (50 toluidine–blue positive cells per 500). Small numbers of eosinophils (<4 of 500) were sporadically (9 of 195 brushes) found in cytospins stained with May-Grunwald-Giemsa stain.

Biopsy specimens

The sections of the nasal mucosa had an average surface area of 1.6 mm^2 and usually showed a lining of ciliated columnar epithelium with or without goblet cells, partially stratified cuboidal epithelium, or both. The lamina propria usually consisted of a looser subepithelial cell-rich layer with most of the mucous glands

TABLE IV. Median cell numbers and 25th percentile and 75th percentile for the various treatment regimens at the end of the run-in period (after 4 weeks and 8 weeks of treatment)

		Run-in		4 weeks		8 weeks	
		Median	25%-75%	Median	25%-75%	Median	25-75%
Epithelium							
CD1	Placebo	55	22-134	23	0-122	50	27-126
	200	52	4-150	0	0-3	3	0-17
	200/400	83	35-110	0	0-16	0	0-3
	400	50	8-129	0	0-0	0	0-0
CD3	Placebo	936	423-1143	488	250-848	347	215-656
	200	623	471-800	115	60-477	145	50-463
	200/400	652	331-1208	192	71-383	65	14-114
	400	403	257-789	151	38-348	210	10-317
CD4	Placebo	386	190-544	255	104-514	187	86-331
	200	486	327-1192	63	14-162	78	10-167
	200/400	453	277-674	195	43-343	30	11-76
	400	336	184-716	20	6-93	33	13-98
CD8	Placebo	518	288-1018	224	129-629	92	37-241
	200	531	156-997	135	102-335	128	57-145
	200/400	448	127-663	141	73-228	24	9-80
	400	310	133-680	69	14-206	24	7-103
CD25	Placebo	20	2-39	15	6-38	20	5-34
	200	0	0-20	4	0-36	4	0-13
	200/400	8,5	0-24	0	0-59	7	0-32
	400	0	0-18	0	0-20	4	0-27
BMK 13	Placebo	0	0-7	0	0-5	0	0-10
	200	0	0-8	0	0-0	0	0-0
	200/400	0	0-0	0	0-0	0	0-0
	400	0	0-1	0	0-0	0	0-0
Tryptase	Placebo	0	0-20	0	0-0	0	0-2
	200	0	0-0	0	0-0	0	0-0
	200/400	0	0-12	0	0-0	0	0-0
	400	0	0-3	0	0-0	0	0-0
Chymase	Placebo	0	0-10	0	0-0	0	0-0
	200	3	0-22	0	0-0	0	0-0
	200/400	2	0-8	0	0-0	0	0-0
	400	0	0-5	0	0-0	0	0-0
IgE	Placebo	7,5	0-45	4	0-38	19	0-75
	200	0	0-6	0	0-0	0	0-14
	200/400	0	0-100	4	0-33	10	0-53
	400	0	0-80	0	0-16	0	0-0
Lamina propria							
CD1	Placebo	4	1-33	5	0-7	7	2.5-30
	200	3	0-9	0	0-1	1	0-4
	200/400	7	3-14	0	0-6	0	0-2
	400	4	1-18	0	0-0	0	0-0
CD3	Placebo	586	446-1104	352	270-613	543	366-688
	200	446	274-804	397	147-537	386	237-814
	200/400	769	495-921	440	253-686	278	199-476
	400	405	226-741	347	271-576	355	125-1137
CD4	Placebo	416	289-644	337	211-451	372	267-749
	200	309	206-536	187	139-518	393	161-748
	200/400	479	319-766	335	161-392	300	187-506
	400	325	162-586	152	73-517	284	204-529
CD8	Placebo	376	200-655	279	188-329	186	111-399
	200	324	140-415	142	92-340	195	123-401
	200/400	292	174-603	296	216-479	155	108-229
	400	329	151-476	136	87-348	208	93-412
CD25	Placebo	10	1-35	12	8-46	30	12-49
	200	0,5	0-5	3	1-3	17	3-38
	200/400	6	0-13	7	0-43	14	6-22
	400	2	0-75	15	1-33	10	5-34

TABLE IV. Cont'd

		Run-in		4 weeks		8 weeks	
		Median	25%-75%	Median	25%-75%	Median	25-75%
BMK13	Placebo	6	0-18	3	1-19	8	1-25
	200	2,5	0-8	0	0-3	0	0-9
	200/400	0	0-3	0	0-13	0	0-2
	400	1,5	0-4	1	0-11	0	0-3
Tryptase	Placebo	94	54-131	39	28-75	50	19-78
	200	86	43-117	18	1-58	17	8-68
	200/400	59	33-94	31	16-39	24	14-37
	400	66	34-79	36	13-55	19	10-35
Chymase	Placebo	86	47-125	73	46-109	53	25-106
	200	69	39-139	59	27-97	46	18-86
	200/400	61	51-105	53	35-63	49	27-66
	400	62	53-75	43	27-67	25	12-37
IgE	Placebo	36	5-98	24	5-79	32	8-121
	200	6	1-43	19	4-37	11	4-27
	200/400	31	17-99	21	3-59	26	6-69
	400	9	1-52	21	14-47	9	0-27

TABLE V. Statistical evaluation after 4 weeks of treatment

	400 vs 200 + 200/400	200 + 200/400 vs placebo	400 vs placebo
Epithelium			
CD 1		↓ ↓	↓ ↓
CD 3		↓	↓ ↓
CD 4	↓		↓ ↓ ↓
CD 8		↓	↓ ↓
CD 25			
BMK 13		↓	
Tryptase		↓	
Chymase			
IgE			
Lamina propria			
CD 1		↓	↓ ↓
CD 3			
CD 4			
CD 8			
CD 25			
BMK 13			
Tryptase		↓	
Chymase			
IgE			

The biopsy data from the FPANS 200 OD group and the data from the FPANS 200 OD for 4 weeks followed by FPANS 200 BD for 4 weeks group are pooled because these groups received the same treatment up to 4 weeks.

Single arrow, $p < 0.005$; *double arrow,* $p < 0.01$; *triple arrow,* $p < 0.001$.

TABLE VI. Statistical evaluation after 8 weeks of treatment

	200 vs placebo	400 vs placebo	200/400 vs placebo	400 vs 200	400 vs 200/400
Epithelium					
CD 1	↓ ↓	↓ ↓ ↓	↓ ↓ ↓	↓	
CD 3	↓	↓	↓ ↓ ↓		
CD 4		↓ ↓	↓ ↓ ↓		
CD 8		↓	↓ ↓	↓	
CD 25					
BMK 13	↓				
Tryptase					
Chymase					↓
IgE		↓			↓
Lamina propria					
CD 1	↓	↓ ↓ ↓	↓ ↓ ↓	↓	
CD 3			↓ ↓		
CD 4					
CD 8					
CD 25					
BMK 13	↓	↓ ↓	↓ ↓		
Tryptase		↓			
Chymase		↓	↓		↓
IgE		↓			↓

Single arrow, $p < 0.05$; *double arrow,* $p < 0.01$; *triple arrow,* $p < 0.001$.

and a deeper collagenous cell-poor layer. All sections were sufficiently deep to assess both layers. The sections were generally of good quality. Two biopsy specimens could not be evaluated because one had been defrosted and one had been misplaced. The mAb supersensitive immunoalkaline phosphatase staining showed red cells against a blue counterstained background. T lymphocytes, small round cells, were abundantly present in the epithelium and the lamina propria. Sometimes clusters of T cells were found in the epithelium or the lamina propria (500 to 1000 cells). The occurrence of these clusters did not differ between the groups. Langerhans cells, large dendritic cells, were found mostly in the epithelium. Only a few were present in the lamina propria. Mast cells were found mostly in the lamina propria and rarely in the epithelium. Eosinophils were rarely present in our material. Sometimes moderate infiltrates were found in the mucosa, but their occur-

rence did not differ among the groups in the first biopsy specimens.

Nasal mucosa

Median cell numbers and 25th percentile and 75th percentile are shown for CD1-, CD3-, CD4-, CD8-, CD25-, IgE-, major basic protein–, tryptase-, and chymase-positive cells in the epithelium and lamina propria in Table IV. Table V (after 4 weeks of treatment) and Table VI (after 8 weeks of treatment) show the results after statistical evaluation for the different biopsy moments and treatment regimens. No significant difference was found between the different groups before treatment (biopsy number 1). A marked effect on the number of Langerhans cells and T cells was seen. The effect of the double-steroid dose was more marked than that of the single dose. No additional effect of 4 consecutive weeks of steroid treatment was found after the first 4 weeks of treatment in the epithelium. In the lamina propria, 4 extra weeks of treatment seemed to affect the mast cells and eosinophils if present.

DISCUSSION

Patients

We were surprised that of the 300 selected patients, only 65 satisfied our condition for inclusion of nasal complaints for more than 1 hour a day. This underscores the importance of the use of nasal symptom scores to characterize patients.

Symptoms

The efficacy of 200 μg of FPANS daily or 400 μg of FPANS daily in treating nasal symptoms in this second-echelon strictly selected group proved to be no greater than that of placebo. This contrasts with previous reports. However, of these early studies, only the study by Malm et al.[6] (n = 22) was placebo-controlled. Half of the patients in that study showed a nasal eosinophilia (patients with nonallergic rhinitis with eosinophilia syndrome), which is known to be associated with a good response to steroids.[25] In our study no eosinophilia was shown. Furthermore, in the study by Malm et al., the reduction of baseline complaints by placebo was larger than the additional effect of steroid therapy. The efficacy of placebo has to be attributed partially to wetting the nose twice a day with the spray.[26] Scadding et al.[9] reported on the clinical efficacy of topical steroids in a combined group of 371 patiens with allergic and nonallergic rhinitis. They concluded that topical steroids are efficacious in the treatment of allergic and nonallergic rhinitis. Unfortunately, no distinction was made between allergic and nonallergic patients as they were pooled in the separate treatment groups. The efficacy of treatment versus placebo was not separately tested for the nonallergic patients. The reported *overall* efficacy might perhaps be attributed to the known clinical efficacy in patients with allergic rhinitis. Furthermore, a significant reduction in nasal eosinophilia was seen in the nonallergic group, which was similar to that seen in the allergic group, again suggesting a substantial number of patients with nonallergic rhinitis with eosinophilia syndrome.

The only significant decrease found in the percentage of symptom-free days was for sneezing, not the most important complaint of our patients. A significant effect was not found for any of the other assessment methods (i.e., VAS, DRC mean sum scores, assessment of nasal symptoms by investigator, and rhinoscopy). A small dose-dependent effect on symptoms, which was not significant, can be seen in the different graphs. Considering the aforementioned results, we believe that the effect of FPANS on nasal symptoms in patients with NANIPER as we selected them is not clinically relevant. We believe that the patients with NANIPER seen by specialists these days do not have a cell-mediated disease.[27] Currently, nasal steroids are often used as the first line of treatment before referring patients to a specialist. It is thus possible that the referred patients with NANIPER are mostly steroid nonresponders, which is in accordance with our clinical experience.

Cells

The concept of NANIPER being caused by a neurogenic inflammation, as presented by Wollf and others,[15] is not supported by our findings. First, we found no differences in the numbers of inflammatory cells between patients and control subjects.[27] Second, there is a lack of efficacy of nasal steroids in this group, whereas these steroids have been reported to be efficacious in induced neurogenic inflammation.[21]

The absence of a correlation between the marked reduction in cell numbers of the immunocompetent cells and nasal complaints could be the result of two different phenomena. Either our groups are too small to measure an effect on nasal complaints, (although our group is larger than those of Malm et al. [n = 22][6] and Pipkorn and Berge [n = 12][8] who did find a significant reduction in nasal complaints) or the reduction in cell numbers by the steroid therapy in NANIPER is not clinically relevant. The reported reductions in cell numbers in response to the steroid treatment in allergic rhinitis are preceeded by an increase of immunocompetent cells in response to the allergic stimulus. In NANIPER, however, no significant differences were found in immunocompetent cell numbers between patients and healthy control subjects.[27] Therefore it is more likely that the absence of a correlation in this study is relevant.

The steroid effect in the nose seems to be cell-specific and not disease-specific. The Langerhans cells seem to be most sensitive to steroid therapy, as in allergic rhinitis.[4] The T cells in the epithelium are also sensitive but to a lesser extent. Although our NANIPER data suggest only a moderate effect on eosinophils and mast cells, which is not in line with the allergy data, this is probably due to the relative absence of these cells in NANIPER when compared with allergic rhinitis. If, even in small numbers, eosinophils and mast cells are present in patients with NANIPER, they are also reduced. There is an additional effect on cells if the dose of FPANS is

doubled after 4 weeks (FPANS OD followed by BD group). This is in agreement with data from Godthelp et al.[4] on patients with perennial allergic rhinitis. The additional effect of the higher dosage of local steroid in NANIPER on the reduction in cell numbers has not been described before. Whether this has implications in the treatment of steroid-responsive patients is questionable. The marked effect of a wetting agent (i.e., placebo) in NANIPER as observed by Malm et al.[6] and Spector[26] is not seen in this study. Our findings as far as the placebo effect is concerned are more in line with those of Scadding et al.[9] This might reflect the change in the NANIPER population seen by today's specialist.

To conclude, the "rhinitis" specialist is increasingly confronted with a nonsteroid-responsive NANIPER group. Doubling the treatment does not have a significant effect on nasal symptoms. Although there is a significant dose-dependent steroid effect on nasal immunocompetent cells, this does not seem to be of clinical relevance.

One must bear in mind that this is a referred and therefore selected group. In a "virgin" (no previous local steroid) patient with NANIPER, local steroids are still the first-line treatment. Topical capsaicin therapy might be a new therapy for the nonsteroid-sensitive group.

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