

Intranasal flunisolide spray as an adjunct to oral antibiotic therapy for sinusitis

Eli O. Meltzer, MD,^a H. Alice Orgel, MD, PhD,^a James W. Backhaus, MD,^b William W. Busse, MD,^c Howard M. Druce, MD,^d W. James Metzger, MD,^e Don Q. Mitchell, MD,^f John C. Selner, MD,^g Gail G. Shapiro, MD,^h Julius H. Van Bavel, MD,ⁱ and Christa Basch, MD^j San Diego, Calif., Madison, Wis., St. Louis, Mo., Greenville, N.C., Jackson, Miss., Denver, Colo., Seattle, Wash., Austin, Texas, and Palo Alto, Calif.

Background: The diagnosis of sinusitis is difficult and there are few controlled studies of customary therapies. In particular, the possible role of topical intranasal steroid as an adjunct to antibiotic treatment has not been evaluated.

Methods: The study was a multicenter, double-blind, randomized, parallel trial in which patients aged 14 years or older were recruited from allergy practices. All patients had maxillary sinusitis documented by radiographs. Treatment consisted of amoxicillin/clavulanate potassium 500 mg combined with nasal spray of either 100 µg flunisolide or placebo to each nostril three times a day for 3 weeks (phase I) followed by administration of flunisolide or placebo nasal spray alone three times a day for 4 weeks (phase II).

Results: Clinical symptoms and signs decreased significantly in both treatment groups during phase I ($p < 0.01$). There was a trend to greater improvement in the patients treated with flunisolide, but only the decrease in turbinate swelling/obstruction was statistically significant at the end of phase I when compared with placebo ($p = 0.041$). Patients' global assessment of overall effectiveness of treatment was higher for flunisolide than placebo after phase I ($p = 0.007$) and after phase II ($p = 0.08$). Maxillary sinus radiographs showed improvement in both treatment groups during phase I ($p < 0.004$) with somewhat greater regression of abnormal findings in patients treated with flunisolide after phase II ($p = 0.066$). However, 80% of radiographs were still abnormal at the end of phase I. All types of inflammatory cells were significantly decreased in nasal cytograms in patients treated with flunisolide in comparison with those treated with placebo. Flare-up of sinusitis during phase II occurred in 26% of patients treated with flunisolide and 35% of those treated with placebo and tended to be more severe in the latter, although these differences were not statistically significant. Adverse events, mainly gastrointestinal symptoms and headache, were similar in both groups and more frequent in phase I than in phase II, (42 vs 15 patients); these side effects were probably due to the antibiotic.

Conclusion: The addition of flunisolide topical nasal spray as an adjunct to antibiotic therapy was most effective in global evaluations, tended to improve symptoms, to decrease inflammatory cells in nasal cytograms, to normalize ultrasound scans, and to aid regression of radiographic abnormalities compared with placebo spray. (*J ALLERGY CLIN IMMUNOL* 1993;92:812-23.)

Key words: Sinusitis, flunisolide nasal spray, amoxicillin/clavulanate potassium, nasal cytologic studies

From ^aAllergy and Asthma Medical Group and Research Center and University of California San Diego Medical School; ^bSan Diego Diagnostic Radiology Medical Group; ^cUniversity of Wisconsin Medical School, Madison; ^dSaint Louis University School of Medicine, St. Louis; ^eSchool of Medicine, East Carolina University, Greenville; ^fMississippi Asthma and Allergy Clinic, Jackson; ^gAllergy Respiratory Institute of Colorado, Denver; ^hDepartment of Pediatrics, University of Washington School of Medicine, Seattle; ⁱAustin Diagnostic Clinic; ^jSyntex Laboratories Inc., Palo Alto.

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Reprint requests: Eli O. Meltzer, MD, Allergy & Asthma Medical Group & Research Center, A P. C., 9610 Granite Ridge Dr., Suite B, San Diego, CA 92123.

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Abbreviations used

t.i.d.: Three times a day
VAS: Visual Analog Scale

Sinusitis is a common medical problem and an important cause of morbidity. In 1989 almost 16 million consultations with a physician were for a condition diagnosed as sinusitis.^{1, 2} Protection against infection of the sinuses is provided by the characteristics of respiratory secretions³ and by the mucociliary system whereby foreign particles, including bacteria, are prevented from entering the sinus cavities through the ostia.⁴ Retention of secretions in the paranasal sinuses caused by reduction of the patency of the ostia is the primary factor in the development of most cases of sinusitis. The size of the ostia is reduced by swelling of the mucous membrane, which may have multiple causes, including nasal allergic disease and infectious rhinitis.⁴ The maxillary sinuses are the most frequently involved.

The patient may complain of the following symptoms: discolored nasal discharge, postnasal drip, sore throat, headache, facial pain, toothache, halitosis, hyposmia, cough that is usually worse when recumbent, fever, and malaise. On physical examination the nasal turbinates may be red and swollen, and tenderness may be present on percussion of the infected sinuses. Purulent secretions are frequently visible in the nose and in the posterior oropharynx. The oropharyngeal mucosa may have an irritated appearance.

Diagnosis of sinusitis is based on the characteristic constellation of symptoms and signs and may be confirmed by radiography. The occipitomeatal or Waters' view radiograph is commonly used for visualizing the maxillary sinuses. Opacification, air-fluid levels, or mucosal thickening greater than 6 mm (4 mm in children) have been shown to correlate with bacterial infection of the maxillary antra.⁵⁻⁷ Follow-up imaging is recommended to exclude persistence of disease.⁵ Evidence of acute or chronic maxillary sinusitis may also be documented by nasal cytologic studies, antral puncture, fiberoptic nasopharyngoscopy, ultrasound, nuclear magnetic resonance imaging, and computerized tomography.⁸⁻¹⁴ The sinus radiograph is still the most commonly used ancillary investigation for diagnosis of bacterial infection of the sinuses.

Treatment of sinusitis consists of nonspecific measures such as increased oral fluid intake,

steam inhalation, and administration of analgesics together with oral or topical decongestants.^{15, 16} Orally administered antibiotics are frequently used, especially in chronic cases or when purulent secretions are present. Various antibiotics have been evaluated, with duration of courses ranging from 7 days to 4 weeks.^{3-7, 16-20} Because β -lactamase-producing organisms are frequently implicated, amoxicillin/clavulanate potassium (Augmentin) is often the antibiotic of choice. Because inflammation and edema of the mucosa of the nasal turbinates and sinus ostia cause obstruction to efficient drainage, it has been suggested that a topical antiinflammatory agent, such as an intranasal steroid, be included in the therapeutic regimen.^{3, 4, 15-18} It has been theorized that by decreasing the inflammatory response and reducing the mucosal swelling, a topical intranasal steroid would promote drainage and increase aeration of the sinuses, hasten the elimination of infectious organisms, and decrease the frequency and severity of recurrences. Evidence that this adjunctive therapy is helpful either for promoting resolution or for preventing recurrences of sinusitis has not previously been addressed in a controlled study.

This study was designed to attempt to answer these questions with the use of intranasal flunisolide. This antiinflammatory topical steroid was administered to patients with roentgenographic evidence of sinusitis who were also treated with an antibiotic. Flunisolide nasal spray is effective not only in decreasing the symptoms caused by the inflammation of allergic rhinitis but also the associated edema and cellular infiltrate,²¹ the obstruction to nasal airflow,²² and the release of inflammatory mediators.²³

METHODS

Study design

The study was a multicenter, randomized, placebo-controlled, parallel group trial in patients older than 14 years of age with symptoms and signs of acute or chronic sinusitis, namely nasal discharge, facial pain, sinus headache, and maxillary sinus tenderness. Patients were recruited in the practices of allergy specialists. All patients had a positive Waters' view radiograph, which was defined as demonstrating one or more of the following: complete opacification, an air-fluid level, or maxillary mucoperiosteal thickening of more than 6 mm in one or both maxillary antra. Patients were eligible for enrollment if they had not used intranasal steroids for 2 weeks before entering the study or orally administered steroids or antibiotics for treatment of sinusitis in the previous 4 weeks. Subjects allergic to penicillin and those with serious disease other than

TABLE I. Analysis of treatment efficacy and other variables

1	Clinical evaluation of sinusitis symptoms (turbinate swelling/obstruction, facial pain, sinus headache) and sinusitis signs (discharge, percussion tenderness) None = 0, Mild = 1, Moderate = 2, Severe = 3
2	Global assessment of treatment efficacy (VAS 0 = no control, 100 = total control)
3	Maxillary sinus x-ray - overall evaluation by VAS, 0 = totally abnormal, 100 = normal.
4	Radiographic measurements of complete opacification, mucosal thickening (mm), air/fluid level in maxillary sinuses
5	Frequency and severity of flare-up of sinusitis symptoms in phase II None = 0 Mild = 1 Moderate = 2 Severe = 3
6	Nasal cytology (two centers)
7	Ultrasound scans (one center)
8	Adverse events

sinusitis were excluded, as were patients with nasal polyps. There was no attempt to determine whether patients had aeroallergen hypersensitivity. The study was approved by the institutional review board at each research center.

At the first visit, details of the current status of sinusitis were obtained. Patients received a physical examination with special emphasis on examination of the nose, including rhinoscopy, and the throat. Symptoms and signs of sinusitis were separately scored for severity on a scale of 0 (none) to 3 (severe) (Table I). An informed consent form was signed. A Waters' view sinus radiograph was obtained, and blood was drawn for a complete blood count with differential count.

A nasal mucosal specimen was obtained by Rhinoprobe (Apotex Scientific Inc., Arlington, Texas) at two of the research centers for nasal cytologic examination. Nasal cytograms were coded and were examined by one blinded technician for neutrophils, eosinophils, basophils, neutrophils, and bacteria. Each cell type was scored semiquantitatively as 0 = none, 1 = few, scattered, 2 = moderate number, 3 = large clumps not covering the field, and 4 = clumps covering all of the field.⁸⁻¹⁰ Each cell type was analyzed for change in score both by comparison of treatment groups at each visit and evaluation of within treatment group changes at each visit.

A-mode ultrasound scans of the maxillary sinuses were performed by one investigator, and the results were read in blinded fashion at one sitting after study completion. The instrument used was an Echoline 1000 (American Electromedics Corp., Hudson, N.H.). Scans were evaluated as normal or abnormal. If abnormal, the presence of fluid and/or mucosal thickening was noted. Mucosal thickening was measured in millimeters of separation between second and third echos.^{11, 12}

Eligible patients were randomized to receive 7 weeks of treatment with either flunisolide 0.025% nasal solution, 2 sprays in each nostril three times a day (t.i.d.) (a total of 300 µg/day) or placebo spray t.i.d. All patients received amoxicillin/clavulanate potassium 500 mg t.i.d. orally for the first 3 weeks (phase I) and continued use of the nasal spray without antibiotic for an additional 4 weeks (phase II).

At the end of phase I and at end point, patients were

reevaluated at the research centers. End point data include information from those patients who completed phase II and also those who entered this phase of the study but were unable to complete the full 4-week period. At the end of phase I and at end point, in addition to the clinical assessments, sinus radiographs, nasal cytologic studies, and laboratory tests were performed as at the first visit. Global evaluations of treatment efficacy, flare-ups of sinusitis, and adverse events were recorded. Ultrasound scans were repeated only at end point.

The three Waters' view radiographs obtained for each patient were sent to a single independent radiologist for interpretation. For the evaluations all radiographs were blinded as to research center, medication group, and sequence. After selection of the film that appeared the most abnormal, the other two films of each patient were graded in comparison. The maximum mucosal thickness in the maxillary sinuses was measured, and the presence or absence of maxillary sinus opacification and air-fluid level were noted.

The radiologist developed a visual analog scale (VAS) for overall evaluation of each (i.e., left and right) maxillary sinus, which ranged from 0 for "totally abnormal" to 100 for "normal," in reference to the percent of sinus volume aerated, taking into account sinus anatomy, radiologic technique, patient position, and other variables. This VAS could be used for comparison of sequential films in the same patient independently of somewhat different patient positioning, which could influence the measurement of mucosal thickness. The VAS would also be independent of sinus size. Calculation of mean population values for sinus "abnormality" was considered more accurate with the use of this scale. This method of reading the radiographs was found to have a reproducibility of $\pm 10\%$ after 46 blinded second interpretations.

The variables that were analyzed for changes within treatment groups and between treatment groups are summarized in Table I.

Statistical methods

Continuous demographic variables were analyzed with two-way analysis of variance with factors for treatment, investigator, and treatment-by-investigator inter-

TABLE II. Baseline demographic and disease characteristics of patients

	Flunisolide group (<i>n</i> = 91)	Placebo group (<i>n</i> = 89)	Total (<i>N</i> = 180)
Age (yr) mean ($\pm$ SEM)	36.2 (1.2)	37.5 (1.5)	36.8 (0.9)
Gender	No. (%) of patients		
Male	39 (43)	48 (54)	87 (48)
Female	52 (57)	41 (46)	93 (52)
Primary diagnosis			
Acute maxillary sinusitis	50 (55)	45 (51)	95 (53)
Chronic maxillary sinusitis	41 (45)	44 (49)	85 (47)
Clinical findings			
Turbinate swelling/obstruction	88 (97)	87 (98)	175 (97)
Nasal discharge	87 (96)	80 (90)	167 (93)
Sinus headache	68 (75)	53 (59)	131 (67)
Facial pain	49 (54)	43 (48)	92 (51)
Sinus tenderness	40 (34)	45 (38)	65 (36)
Radiographic abnormality			
Mucosal thickness $\geq$ 6 mm	73 (80)	67 (75)	140 (78)
Opacification	29 (32)	31 (35)	60 (33)
Air-fluid level	27 (30)	22 (25)	49 (27)

action. For categorical data, the Cochran-Mantel-Haenszel test controlling for investigator was used to detect differences between treatment groups. For analysis of between-treatment efficacy variables continuous measurements, such as VASs, were evaluated with the Cochran-Mantel-Haenszel mean test controlling for investigator. For categorical data Cochran-Mantel-Haenszel mean tests were used at baseline controlling for investigator, at the end of phase I and at end point controlling for investigator and baseline, and at end point controlling for investigator and end of phase I. End point analyses included patients who completed phase II and patients who entered phase II but did not complete the 4-week period. Within-group improvements were tested at the end of phase I with reference to baseline, at end point with reference to baseline, and at end point with reference to the end of phase I with the signed-rank test.²⁴ All analyses were performed with the PC SAS (SAS Institute, Cary, N.C.).²⁵ A sample size of 80 patients per treatment group was selected to provide 80% power at the 0.05 level (two-tailed tests).

RESULTS

A total of 180 patients satisfied the enrollment criteria at the eight study centers. Of these, 175 were randomized to groups and entered the treatment phase with either flunisolide (*n* = 89) or placebo (*n* = 86) spray in addition to amoxicillin/clavulanate potassium. The demographic data and the disease characteristics of the patients at the start of the study are summarized in Table II. There were no significant differences in demographic characteristics among treatment groups or research centers. The patients were almost

equally divided into groups of those who had infrequent attacks (acute sinusitis) and those who had frequent recurrences and longer duration of symptoms (chronic sinusitis). At entry to the study, nearly all patients had multiple symptoms and signs, including nasal obstruction, discolored nasal discharge, and facial pain or headache. For most patients the symptoms and signs at baseline were mild or moderate, but approximately 10% of patients had severe turbinate swelling with marked nasal obstruction or severe sinus headache. At baseline, patients in the flunisolide group tended to have headaches that were more severe, of longer duration, and with greater frequency ($p = 0.08$, $p = 0.029$, and $p = 0.05$, respectively) in comparison with patients in the placebo group. There were no other significant differences in baseline symptoms between treatment groups.

At the end of phase I, which included the 3 weeks of antibiotic therapy, there were statistically significant decreases in all clinical parameters in comparison with baseline in both flunisolide and placebo treatment groups ($p < 0.01$). These data are presented in Table III. Changes within groups between the end of phase I and end point were small; only facial pain in the patients treated with flunisolide decreased significantly ($p < 0.026$) during phase II. The mean scores for turbinate swelling/obstruction at baseline, end of phase I, and end point for flunisolide and placebo treatment groups are presented in Fig. 1 with the p values for differences in turbinate swelling/obstruction scores within treatments at each evalu-

TABLE III. Mean changes in symptom and sign scores baseline to end of phase I in the two treatment groups

	Flunisolide (n = 74)			Placebo (n = 74)			pt Mean score FN vs PL
	MBS	MCB	p* Value	MBS	MCB	p* Value	
Turbinate swelling/obstruction	1.7	-0.53	<0.0001	1.7	-0.31	0.0045	0.041
Facial pain	0.82	-0.62	<0.0001	0.71	-0.39	0.0008	0.36
Headache severity	1.3	-0.88	<0.0001	1.0	-0.64	<0.0001	0.82
Discharge	1.5	-0.49	<0.0001	1.5	-0.31	0.0027	0.36
Percussion tenderness	0.45	-0.26	0.0013	0.58	-0.35	0.0023	0.054

MBS, Mean baseline score; MCB, mean change baseline to end phase I; FN, flunisolide; PL, placebo.

*p values within treatment group change, sign-rank test.

†p value Cochran-Mantel-Haenszel mean score statistic (flunisolide vs placebo).

ation visit. There was statistically greater improvement in the turbinate swelling/obstruction score in the flunisolide-treated group in comparison with the placebo-treated group ($p = 0.041$) at the end of phase I. However, 80% to 90% of patients demonstrated some turbinate swelling at both the end of phase I and at end point. In contrast, sinus headache scores were relatively more improved (Fig. 2). Approximately 75% of patients who completed phase I were free of headache at that evaluation, with no significant differences between treatment groups. For other clinical variables there was a trend to greater improvement in the flunisolide group, but the differences between treatment groups were not statistically significant (Table III).

In overall global assessments of the efficacy of sinusitis therapy, which were scored on VASs by patients, the mean scores were significantly higher in the flunisolide group compared with the placebo group at the end of phase I (69.4 vs 56.3, $p = 0.007$). At end point, patients treated with flunisolide still scored overall efficacy of treatment higher than patients treated with placebo, but the difference was not statistically significant (60.9 vs 50.6, $p = 0.08$). At both evaluation times and in both treatment groups, assessment of efficacy of sinusitis therapy ranged from no relief to complete relief.

When patients entered the study, all maxillary sinus radiographs were abnormal as required by the protocol. During screening at one center, a total of 104 patients with clinical symptoms and signs of sinusitis had Waters' view sinus radiographs both to confirm the clinical diagnosis and as a screening procedure for enrollment in the study. Of these only 32 fulfilled the rigorous radiographic criteria for eligibility. The abnormal-

ities included mucosal thickening of 6 mm or more in one or both maxillary sinuses in 75% to 80% of patients and complete opacification or air-fluid level in one or both sinuses each in approximately one third of patients (Table II). Approximately 90% of patients had radiographic abnormalities reported for both maxillary sinuses. There were no significant differences in radiologic findings between treatment groups at baseline. Mean VAS radiologic scores at baseline were 66.7 and 66.9 in the flunisolide and placebo groups, respectively (Table IV).

Radiographic findings were tabulated and analyzed for left and right antra for changes between baseline and the end of phase I, that is, after 3 weeks of treatment with flunisolide or placebo intranasal spray concomitantly with the antibiotic, and for changes that occurred between the end of phase I and end point (i.e., after an additional period of treatment with one of the intranasal sprays alone). Because there were no significant radiographic differences between left and right antra, mean results were calculated for both antra combined. Visual analog scores, presence or absence of opacification, and the maximum antral mucosal thickness were analyzed, as well as presence and change in air-fluid levels.

At the end of phase I there was statistically significant improvement in mean visual analog radiologic scores and in air-fluid levels compared with baseline values in both treatment groups. Mean mucosal thickness also decreased, but the changes were not statistically significant. There were no significant differences between flunisolide and placebo treatment groups at the end of this phase. Between the end of phase I and end point (i.e., the antibiotic-free phase), mean visual analog scores continued to improve slightly

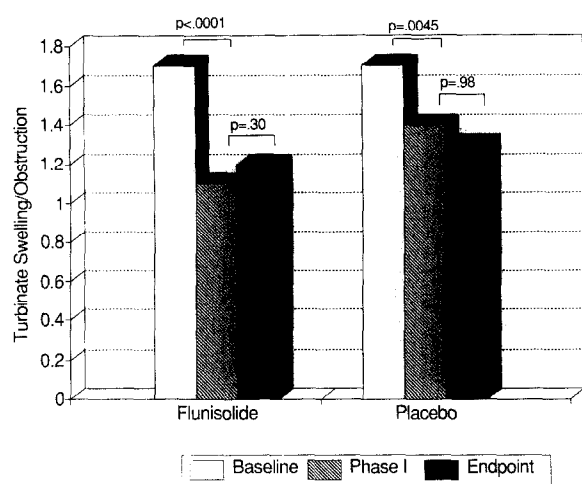


FIG. 1. Mean turbinate swelling/obstruction score in patients treated with flunisolide and placebo at baseline, end of phase I, and end point.

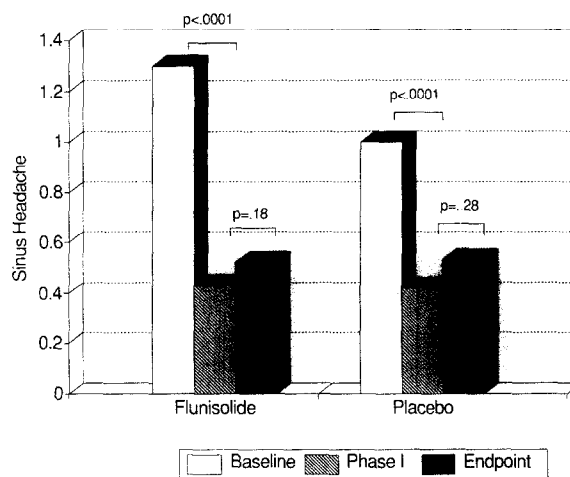


FIG. 2. Mean sinus headache score in patients treated with flunisolide and placebo at baseline, end of phase I, and end point.

TABLE IV. Radiography: Overall visual analog scale, antral mucosal thickness, and air fluid level of the maxillary antra

	Baseline		End of phase I		Mean change baseline to end phase I		Mean change end phase I to end point	
	FN	PL	FN	PL	FN	PL	FN	PL
N	78	74	72	70	72	70	59	61
Mean of left and right antra — visual analog scores*								
Mean	66.7	66.9	74.3	74.7	9.0	8.4	1.3	-3.1
p Value†					0.001	<0.0001	0.73	0.22
p Value‡	0.94		0.82		0.98		0.066	
Mean of left and right antra mucosal thickness (maximum) (mm)§								
Mean	7.5	7.6	6.2	6.9	-1.6	-0.91	-0.74	0.58
p Value†					0.066	0.080	0.26	0.56
p Value‡	0.87		0.43		0.50		0.073	
Mean of left and right antra air/fluid height mm								
Mean	3.3	2.1	0.69	1.1	-2.9	-1.2	0.53	-0.46
p Value†					<0.0001	0.012	0.29	0.33
p Value‡	0.22		0.45		0.096		0.016	

FN, Flunisolide; PL, placebo.

*Visual analog scale: 0 = totally abnormal, 100 = normal.

†Within treatment group change, signed-rank test.

‡Cochran-Mantel-Haenszel mean score statistic (between treatment groups).

§Mucosal thickness greater than 30 mm was rated as opacification.

in the flunisolide treatment group ($p = 0.066$) but deteriorated in the placebo spray group. Similarly, mean changes in mucosal thickness at end point favored the flunisolide treatment group ($p = 0.073$). These results are presented in Table IV. However, the sinus radiographs had a normal appearance in only approximately 20% of patients after 3 weeks of antibiotic therapy.

Flare-ups of sinusitis between the end of phase I and end point (i.e., after completion of anti-

otic therapy) occurred in 26% and 35% of patients in the flunisolide and placebo groups, respectively. The flare-ups occurred earlier and more patients had symptoms that were moderately severe in the placebo group than in the flunisolide group (Fig. 3). However, these differences were not statistically significant.

Mucosal samples for nasal cytologic examination were taken at two of the research centers. Evaluable mucosal samples were obtained from

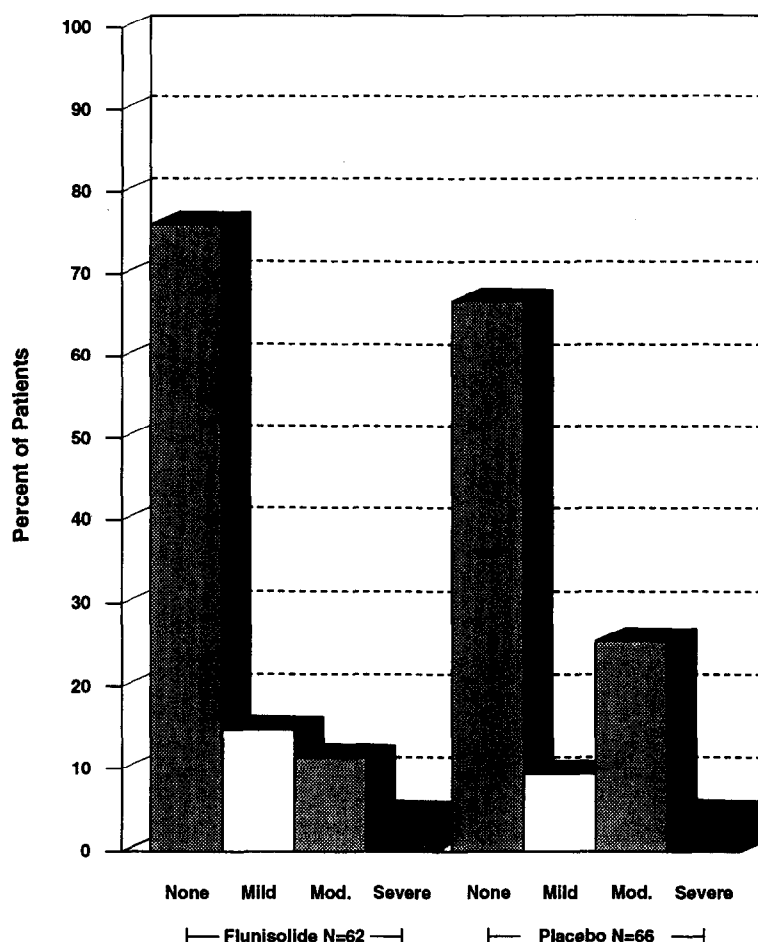


FIG. 3. Severity of flare-up of sinusitis symptoms between the end of phase I and end point.

64 patients at baseline, from 50 patients at the end of phase I, and from 41 patients at end point. Approximately half of the samples at each visit were from patients in each treatment group.

At baseline neutrophils were present in the nasal smears of 92% of patients; in approximately one third of the patients, they were numerous with "large clumps covering the field" in both treatment groups. At end point the score was significantly better in the flunisolide group ($p = 0.034$). More patients treated with flunisolide had "few" neutrophils (50% vs 17% in the placebo group) and fewer patients had clumps covering the field (17% vs 35% in the placebo groups) at end point. The within-treatment changes from baseline to end point were significant only in the flunisolide group ($p = 0.032$).

Eosinophils were present in the cytograms of 72% of patients at baseline and were numerous in approximately 20% in each treatment group. At the end of phase I eosinophils were present in

35% of patients treated with flunisolide and 60% of patients treated with placebo ($p = 0.055$). The within-treatment decrease from baseline to end point was significant only in the flunisolide group ($p = 0.0044$).

Basophils, in comparison with neutrophils and eosinophils, were present in the cytograms at baseline in fewer patients (45% of patients in each treatment group). There was a significant decrease in the basophil score in the patients treated with flunisolide in comparison with those treated with placebo at end point ($p = 0.040$). Within-treatment decrease was significant in the flunisolide-treated group ($p = 0.013$).

Bacteria were noted in five cytograms in the flunisolide group and 11 cytograms in the placebo group at baseline. At the end of phase I, bacteria were present in the cytograms of two patients in the flunisolide group and four patients in the placebo group.

The ultrasound scanning procedure was performed by one investigator. Of 26 patients who

TABLE V. Adverse events

	Phase I (spray & antibiotic)		Phase II (spray only)	
	FN (n = 89)	PL (n = 86)	FN (n = 65)	PL (n = 69)
Any adverse events	60 (67)	50 (58)	24 (37)	35 (51)
Headache	23 (26)	19 (22)	10 (15)	13 (19)
Digestive system	19 (21)	12 (22)	2 (3)	8 (12)
Diarrhea	14 (16)	14 (16)	1 (2)	2 (3)
Nausea	7 (8)	7 (8)	2 (3)	2 (3)
Abdominal pain	4 (4)	1 (1)	1 (2)	0
Taste perversion	9 (10)	7 (8)	0	1 (1)
Vaginitis	7 (8)	4 (5)	0	0

underwent baseline examination, 22 completed all evaluations. There were no significant differences at baseline between treatment groups. The within-group changes from baseline to end point were significantly better in the flunisolide group ($p = 0.046$) and showed a trend to improvement in the placebo group ($p = 0.10$).

Complaints of at least one adverse event were made by approximately two thirds of the patients during phase I and half of the patients during phase II (Table V). Most of the complaints could be attributed to the sinusitis itself, to lack of efficacy of therapy, or to side effects of antibiotic therapy. During phase II, headache was the most frequently reported adverse event. There were no significant differences in adverse events between patients treated with flunisolide and those treated with placebo.

Data from 148 of the 175 patients who started therapy (85%) were available for efficacy analysis at the end of phase I and 128 (69%) at end point. A total of 27 patients terminated prematurely in phase I; 19 of these withdrew because of adverse events, primarily gastrointestinal symptoms caused by the antibiotic. Eight patients withdrew during phase I because of ineffectiveness of treatment. During phase II, four patients withdrew because of adverse events and 10 because of ineffectiveness of treatment or recurrence of symptoms. The remaining six early withdrawals in phase II were for intercurrent illness (two patients) or for administrative reasons. There were no significant differences between treatment groups in the reasons for withdrawal.

Hematology values were within normal limits at the baseline visit and at the end of the study except for a mild eosinophilia in 4% to 10% of patients in pretreatment and posttreatment cell counts. Neutrophils and lymphocytes were within the normal ranges.

DISCUSSION

"Sinusitis" is a common complaint; patients present with symptoms that include facial pain, headache, nasal congestion, and discolored discharge. It frequently occurs after a viral upper respiratory infection. If symptoms do not resolve in a few days either spontaneously or with over-the-counter oral antihistamines or oral or topical decongestants,^{2, 15-18} the patients may consult a physician. The diagnosis of sinusitis is usually made on the basis of history and physical examination with no specific additional evaluations performed. A brief course of antibiotic is usually prescribed. The symptoms may respond to therapy, but recurrences are frequent. Because obstruction of the sinus ostia appears^{4, 15-17} to be a major etiologic factor in infectious sinusitis and because nasal obstruction is a major complaint, physicians have been prescribing a topical intranasal glucocorticosteroid to decrease the inflammatory swelling.^{3, 4, 15-18} However, there are no data to support the use of intranasal topical corticosteroids as an effective adjunct to antibiotic therapy.¹⁵⁻¹⁷

In one study of 50 patients with chronic anterior or posterior purulent nasal discharge, 20 were treated with topical dexamethasone and decongestant sprays, 20 with topical neomycin in addition, and 10 with matched placebo sprays or propellants alone. Significantly more patients who received the active treatments demonstrated improvement in symptoms in comparison with those who received placebo. The authors concluded that improving sinus draining permitted host mechanisms to recover and that topical antibiotics added no additional benefit. However, systemic antibiotics were not used.²⁶ In another study of 80 allergic children with asthma, 4 to 14 years of age, sinus radiographic abnormalities were detected in 55 patients. The findings of mucosal thickening of

more than 2 mm, opacification or air-fluid level were defined as abnormal radiographs. Those children with purulent postnasal drip ($n = 13$) were treated with oral ampicillin, oral triprolidine with pseudoephedrine hydrochloride syrup, and intranasal phenylephrine drops. In 42 children without purulent drainage, the oral ampicillin was replaced by intranasal beclomethasone spray for 1 month together with phenylephrine and oral triprolidine with pseudoephedrine. In both treatment groups sinus radiographs showed improvement with a decrease in severity of the asthma. However, the presence of bacterial sinusitis was not adequately documented, and all children received topical decongestant and oral antihistamine with decongestant so that the role of the intranasal beclomethasone could not be adequately assessed.²⁷ In both of these studies, it was concluded that systemic antibiotics were not required.

In one study the influence of topical intranasal budesonide spray for 3 months was compared with placebo spray in 40 patients with chronic sinusitis. All patients were treated with oral erythromycin for 7 days and underwent antral lavage at the start of the study and after 7, 14, and 90 days of therapy. The patients who received budesonide had significantly greater reduction in facial pain. All patients had received at least one antral lavage in the past 2 years, with a mean number of 9.6 lavages in the budesonide group and 10 lavages in the placebo groups.²⁸ A comparison of sinus irrigations for 11 days with tixocortol pivalate and neomycin or neomycin alone in patients with sinusitis resulted in reduced nasal obstruction in both allergic and nonallergic patients who received the topical corticosteroid.²⁹ It is not possible to determine whether these patients represented subpopulations with sinusitis different from those described in this study. Repeated antral lavages or irrigations constituted different therapies from those evaluated in this study.

Systemic antibiotics are generally recommended for therapy of sinusitis symptoms that last for more than 1 week.^{3-7, 16-20} In this study amoxicillin/clavulanate potassium, 500 mg t.i.d. for 3 weeks, was prescribed for all patients. The paucity of controlled studies for optimal therapy of bacterial sinusitis and the lack of data concerning the role of topical steroids prompted the conduct of this study.

Documenting the diagnosis of bacterial sinusitis is not simple. The maxillary sinuses are nearly

always affected, although other sinuses may also be involved. It has been clearly demonstrated that the types of bacteria cultured from the nose and the nasopharynx correlated poorly with those obtained from the sinus cavities.^{5, 7, 19, 30} Furthermore, antral puncture for diagnosis is not a routine office procedure. Waters' view radiographs are useful for visualization of the maxillary sinuses. Although mild mucosal thickening may be demonstrated in noninfectious inflammatory conditions, Waters' view sinus radiographs showing maxillary sinus mucosal thickening of 6 mm or more, opacification, or presence of an air-fluid level correlate well with the presence of bacterial infection in the sinuses.^{5, 6} A positive Waters' view radiograph with these criteria was a requirement for participation in this study and was obtained in approximately one third of patients screened who presented with typical, moderately severe symptoms and signs of maxillary sinusitis. Some of the patients who did not qualify for the study had lesser degrees of maxillary mucosal thickening and may nonetheless have had bacterial sinusitis. Other patients with similar symptoms and signs had completely normal radiographs. The cause of the symptoms in those patients is not known, but in some, symptoms may have been due to ostiomeatal complex disease, which was not visible on plain sinus films.¹⁸

In this study population turbinate swelling with nasal obstruction and nasal discharge were the predominant findings; sinus headache, facial pain, and sinus tenderness were present with decreasing frequency. Most patients had more than one of these symptoms or signs; turbinate swelling with nasal obstruction and headache were the symptoms most frequently rated severe.

After the 3 weeks of treatment with oral amoxicillin/clavulanate potassium, 500 mg t.i.d., together with either flunisolide or placebo nasal spray t.i.d. (phase I), all clinical findings decreased significantly ($p < 0.01$). There was little further improvement in symptoms and signs during phase II, supporting the view that antibiotic is an important therapeutic modality for sinusitis. At the end of phase I, the flunisolide-treated group had significantly lower scores than the placebo group for turbinate swelling/obstruction ($p = 0.041$) and greater decrease in sinus tenderness ($p = 0.054$). For other symptoms and signs there was a trend toward greater improvement in patients treated with flunisolide compared with those treated with placebo, but the differences were not statistically significant.

Global assessment by patients of overall effectiveness of treatment was significantly higher in patients treated with flunisolide at the end of phase I ($p < 0.007$) in comparison with those treated with placebo. Statistically, the greatest difference between treatment groups was demonstrated by this subjective assessment; it indicates that treatment with topical flunisolide concomitantly with antibiotic provided greater relief than treatment with antibiotic alone. At the end of phase II the difference between treatment groups was less ($p < 0.08$), perhaps because nasal obstruction was no longer causing major discomfort in either treatment group.

Some of the symptomatic relief in both treatment groups may have been due to the nonspecific beneficial effect of a nasal spray.³¹ A saline spray is frequently recommended as an adjunct to the specific therapy of sinusitis.^{3, 15, 16} However, the trend toward greater symptom relief in the patients treated with flunisolide in comparison with those receiving placebo, especially the significant decrease in turbinate swelling, may reflect a direct antiinflammatory effect of the topical steroid spray on the edematous nasal tissues. This could be efficacious whether the swelling was due directly to the infectious process²⁹ or to inflammation for other reasons, for example, allergic disease or nonallergic rhinitis with eosinophilia syndrome.³²

Maxillary sinus radiographs showed statistically significant improvement toward normal at the end of phase I in both treatment groups, with no significant differences between them. Between the end of phase I and end point there was a slight continuing improvement in patients treated with flunisolide and some deterioration in those treated with placebo ($p = 0.066$). Air-fluid levels also decreased significantly in both treatment groups at the end of phase I. The decreases in mucosal thickness were not statistically significant. Approximately 80% of patients had persistence of abnormal radiographs at the end of the antibiotic treatment period. This evidence of continuing antral inflammation despite symptom relief may explain, at least in part, the frequency of recurrence of sinusitis. It also suggests that many of the patients in this study had chronic disease (Table II). Continuing presence of bacteria in cultures of antral aspirates after antimicrobial therapy has been previously reported⁴ and may be another reason for recurrence of symptoms. In this study population recurrences of sinusitis occurred in 26% of patients treated with flunisolide

and 35% of those treated with placebo despite 3 weeks of therapy with amoxicillin/clavulanate potassium, 500 mg t.i.d. Recurrences tended to occur earlier and to be more severe after discontinuation of antibiotic in the placebo group than in the flunisolide group.

The main adverse events that were reported reflected in part the gastrointestinal effects of amoxicillin/clavulanate potassium and in part continuing symptoms caused by ongoing sinusitis.

Skin tests were not performed specifically for this study, which was conducted in the practices of allergy specialists. The finding of eosinophils in the nasal smears of approximately 70% of patients in two research centers supports the probability that most of the patients were allergic or had nonallergic rhinitis with eosinophilia syndrome. Eosinophils are not found in nasal smears of normal subjects. This result also demonstrates that increased eosinophils are detectable in subjects with infectious sinusitis in nasal mucosal samples taken by Rhino-probe. In contrast, eosinophils were not observed in blown nasal secretions in allergic children who had sinusitis.^{20, 33} The eosinophil scores in the nasal cytograms significantly decreased in the flunisolide treatment group compared with the placebo group in which there was no significant change during treatment. The presence of documented sinusitis did not interfere with this effect of topical intranasal steroids on nasal cytologic studies, which has previously been reported in allergic subjects.^{22, 34, 35} Neutrophil and basophil scores were also significantly improved in the patients treated with flunisolide in comparison with those treated with placebo. These decreases in inflammatory cells may be related to symptomatic improvement.

Sinusitis appears to be more common in allergic individuals than in the general population,^{20, 33, 36} but few prevalence data are available. In a study of sinus tissue obtained during surgery for treatment of chronic sinusitis, the tissues from patients with asthma and/or allergic rhinitis were extensively infiltrated with eosinophils. There was a strong association between the presence of extracellular deposition of major basic protein and damage to the sinus mucosa. These findings are consistent with the view that allergic inflammation in the sinuses predisposes patients to bacterial infection.³⁷

A-mode ultrasound has been used to evaluate the presence of fluid and mucosal thickening in the maxillary sinuses.^{11, 12} The methodology has been considered reliable for the detection of fluid

but more questionable regarding mucosal thickening. Of the many published reports in which this modality was used, no previous studies have included sequential measurements to assess response to therapy. The observation that the flunisolide group displayed greater improvement than the placebo group suggests that A-mode ultrasound may sometimes be a useful method for noninvasively evaluating responses to medication regimens; however, it is not generally as useful as radiographs.

To summarize our conclusions, the major improvements in sinusitis symptoms and signs occurred in both treatment groups at the end of phase I, that is, after concomitant treatment with antibiotic and nasal spray. The main improvements in radiographic findings were also seen at the end of phase I. The addition of flunisolide topical nasal spray as an adjunct to antibiotic for the treatment of sinusitis was judged the most effective treatment in the global evaluation and tended to improve symptoms, to decrease inflammatory cells in nasal cytograms, to normalize ultrasound scans, and to aid regression of radiographic abnormalities compared with placebo spray. There were no specific adverse effects associated with the addition of the topical corticosteroid. These results indicate that this modality may be a useful adjunct to antibiotic therapy in some patients. However, despite symptomatic improvement in the majority of patients, many had continuing symptoms, radiographs remained abnormal in most patients, and there were frequent recurrences. These results suggest that there is still a critical need for further study of the diagnosis and therapy of sinusitis.^{16, 38}

Future studies might include further characterization of the study populations, the use of computerized tomography for diagnosis and follow-up of sinusitis, evaluation of longer courses of antibiotics, and evaluation of oral steroids together with antibiotics, as well as additional studies to document the role of topical intranasal steroids.

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