Short communication

Onset of action of mometasone furoate nasal spray (NASONEX®) in seasonal allergic rhinitis

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Background: Mometasone furoate nasal spray (MFNS, NASONEX®), is a new synthetic corticosteroid with considerable efficacy in the treatment of seasonal and perennial rhinitis and less than 0.1% systemic absorption. This study was designed to evaluate the time of onset of action of MFNS. The subjects were evaluated over the course of 2 weeks during the spring allergy season.

Methods: The effects of MFNS 200 μg given once daily for 2 weeks were evaluated in a randomized, multicenter, double-blind, placebo-controlled study in 201 patients with seasonal allergic rhinitis. Clinically significant onset of action was assessed prospectively by special patient diary cards kept during the first 3 days of treatment.

Results: By 12 h after initial dosage (the earliest evaluation), 28% of patients in the MFNS group experienced clinically significant relief, compared with 13% of those given placebo ($P = 0.01$). Median time to at least moderate symptom relief in patients who received MFNS was 35.9 h, compared with more than 72 h in patients given placebo ($P < 0.01$). By 72 h, 64% of the patients receiving MFNS experienced at least moderate relief, compared with 40% of those treated with placebo ($P < 0.01$). Both patient and physician ratings of symptom severity, response to treatment, and overall condition of rhinitis indicated significant ($P < 0.01$) superiority of MFNS over placebo. MFNS was well tolerated, with adverse events comparable to placebo.

Conclusions: MFNS provided rapid onset of clinically significant symptom relief in patients with seasonal allergic rhinitis.

Intranasal corticosteroids are generally considered to have broad application for control of the symptoms of allergic rhinitis (1, 2). Although corticosteroids have demonstrated good efficacy in the management of nasal symptoms of seasonal and perennial allergic rhinitis (3–5), many physicians still consider corticosteroids second-line agents because of concerns about their safety and the perception that these drugs are slow-acting(2, 6).

Mometasone furoate, a synthetic glucocorticoid, has an oral bioavailability of ≤0.1%, lower than that of any corticosteroid currently marketed for the treatment of allergic rhinitis (7). In *in vitro* systems, mometasone furoate was more potent than beclomethasone dipropionate in inhibiting synthesis and release of proinflammatory cytokines, including leukotrienes, interleukins-1, -5, and -6, and tumor necrosis factor alpha (8, 9). Mometasone furoate nasal spray (MFNS, NASONEX®) has been shown to be efficacious in the treatment of both seasonal and perennial allergic rhinitis (10, 11).

The objective of the present study was to determine for MFNS the onset of clinically significant (at least moderate) relief of nasal symptoms due to seasonal allergic rhinitis. Generally, onset of clinical action of corticosteroid nasal sprays for the treatment of rhinitis is difficult to delineate. Determination of this parameter requires a prospective definition of clinically significant symptom relief. Furthermore, in contrast to studies performed in a special pollen chamber, this trial was conducted in patients who were symptomatic as the result of natural exposure to aeroallergens.

Material and methods

Patients

This was a placebo-controlled, double-blind study conducted during the spring allergy season of 1994. Patients were at least 12 years of age and had a history of seasonal allergic rhinitis for at least 2 years, verified by the presence of a positive skin prick test to an appropriate seasonal allergen. All patients were symptomatic at both screening and baseline evaluations and were free of any other clinically significant disease. Nonpregnant women of childbearing age were required to use an effective birth control method for at least 3 months before screening and for the duration of the study. Patients – or parents of patients under the age of 18 – provided written informed consent, and institutional review board approval was obtained.

Excluded from the study were patients with asthma requiring the use of inhaled or systemic corticosteroids, sodium cromolyn, or nedocromil; patients with any significant disease having the potential to interfere with the study; and patients with any clinically relevant abnormal sign or laboratory test reading outside the normal range. Also excluded were pregnant or breast-feeding women; patients on immunotherapy (other than maintenance treatment); patients with upper respiratory or sinus infection or any abnormality that interfered with nasal airflow; patients allergic to corticosteroids or who had recently used any medication that could affect the course of seasonal allergic rhinitis; patients dependent on nasal, oral, or ocular decongestants; and patients with rhinitis medicamentosa.

Evaluations

At the baseline visit (2–7 days after the screening visit), symptoms of allergic rhinitis were evaluated to establish baseline symptom severity scores. At both the screening and baseline visits, patients were required to have at least moderate (score of ≥2) nasal congestion, a combined nasal symptom severity score of ≥7, and a physician-rated overall condition of at least moderate severity (score of ≥2). Patients who met the entry criteria were then assigned to receive 14 days of treatment with either MFNS (two sprays per nostril= 200 μg once daily) or placebo in accordance with a computer-generated random code. Compliance was evaluated at each visit by asking patients whether they had taken their medication as instructed, by reviewing diary cards for times of medication usage, and by examining the patient's drug supply. Any problems with compliance were reviewed with the patient.

Efficacy assessment

Onset of action of MFNS was determined from special diary cards completed by the patients for the first 3 days of the study. Patients were asked to record information on symptomatology twice daily at the same time of day (each morning and evening). In addition, at the baseline visit, patients received a special diary card for the first 72 h of study drug administration to record the response to therapy (twice daily) and the time the patient first experienced at least moderate relief (i.e., noticeable improvement in their nasal symptoms). During these first 72 h, patients were contacted daily by telephone to reinforce compliance with both special and regular diary card completion.

Symptom severity (0= none [no signs or symptoms evident]; 1= mild [signs or symptoms present, but minimal and easily tolerated]; 2= moderate [signs or symptoms bothersome, but tolerable]; and 3= severe [signs or symptoms hard to tolerate, possibly causing interference with daily activities/sleeping]) was rated by physicians at clinic visits on days 4, 8, and 15. Nasal symptoms included stuffiness/congestion, rhinorrhea, nasal itching, and sneezing. Non-nasal symptoms were itching/burning eyes, tearing/watering eyes, redness of the eyes, and itching of the ears/palate. At each clinic visit, the patient and physician evaluated overall condition (see rating scale for symptom severity) and response to therapy (5= no relief [nasal symptoms unchanged or worse]; 4= slight relief [nasal symptoms present, only slightly improved]; 3= moderate relief (nasal symptoms present, may be troublesome, but noticeably improved]; 2= marked relief [nasal symptoms present, but greatly improved, scarcely troublesome]; and 1= complete relief (virtually no nasal symptoms present]).

Safety assessment

At each clinic visit, the investigator judged the relationship of any adverse event as unrelated, or possibly or probably related to treatment. Clinical laboratory tests, including complete blood count, blood chemistry, and urinalysis, were carried out at screening and on day 15.

Data analysis

Patient demographics of the MFNS and placebo groups were compared by analysis of variance for continuous variables and by categoric linear models for discrete variables. The primary efficacy end point, time to onset of at least moderate symptom relief, was analyzed with the long-rank test. Raw scores and changes from baseline for total and individual symptom scores, as well as patients' and physicians' evaluations of symptoms, overall disease condition, and response to treatment, were considered secondary efficacy variables and were evaluated by analyses of variance.

Results

Patient demographics

A total of 201 patients was enrolled at five centers. One patient in the placebo group dropped out after receiving the first dose and was lost to follow-up. Therefore, 200 patients were included in the safety analysis, and demographic data for them are summarized in Table 1. One additional patient in the placebo group and two patients who received MFNS were excluded from the efficacy analysis for noncompliance, failure to meet entry criteria, or both. Except for a slight difference (16 *vs* 19 years, $P=0.05$) in duration of seasonal allergic rhinitis in the placebo group, no significant difference for any variable was noted between groups. The mean age of patients in each group was 31 years, and women slightly outnumbered men.

Onset of action

MFNS exhibited a rapid onset of action. Within 12 h of the first dose (the earliest evaluation), 28% of MFNS patients and 13% of those given placebo experienced clinically significant (at least moderate) symptom relief ($P=0.01$). A

Table 1. Patient demographics

	Overall		
	MFNS (*n*= 101)	**Placebo** (*n*= 99)	**Treatment** *P* value
Age (years)			
Mean	31	31	0.78
Range (minimum–maximum)	12–56	12–59	
Sex			
F	60	51	0.26
M	41	48	
Race			
White	88	87	0.93
Black	9	10	
Other	4	2	
Weight (lb)			
Mean	160	167	0.24
Range (minimum–maximum)	93–295	72–275	
Duration of condition (years)			
Mean	16	19	0.05
Range (minimum–maximum)	2–44	2–55	
Duration of this episode of seasonal allergic rhinitis (days)			
Mean	22	22	0.82
Range (minimum–maximum)	3–61	3–61	
Perennial allergic rhinitis			
No	52	57	0.36
Yes	49	42	
History of asthma			
No	80	86	0.09
Yes	21	13	

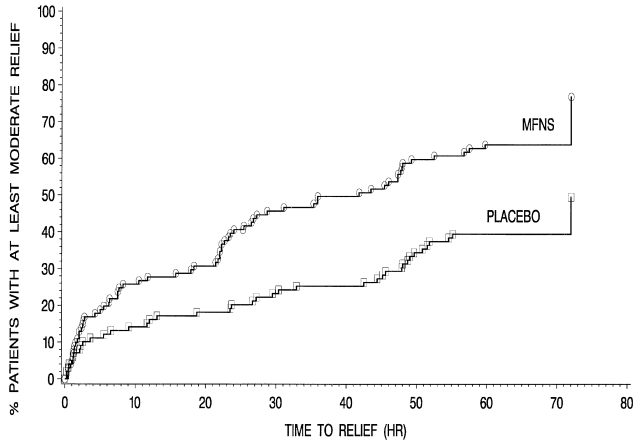

Figure 1. Cumulative percentage of patients achieving at least moderate relief.

total of 64% of patients who received MFNS experienced at least moderate symptom relief within 72 h of initiation of treatment, compared with 40% of those given placebo (Fig. 1) ($P<0.01$). The median time to onset of at least moderate symptom relief was 35.9 h for the MFNS group, compared with more than 72 h for those given placebo ($P<0.01$). The proportion of MFNS-treated patients achieving at least moderate relief was significantly greater ($P\leq0.01$) than that for placebo at all time points except the morning of day 2 of treatment.

Patient diary assessments

Average diary scores over the 2 weeks of dosing indicated that total nasal symptom severity decreased by an average of 39% for MFNS patients compared with 20% for those who received placebo ($P<0.01$). Overall severity score for combined nasal and nonnasal symptoms was reduced by 37% for patients who received MFNS compared with 22% for those given placebo ($P<0.01$).

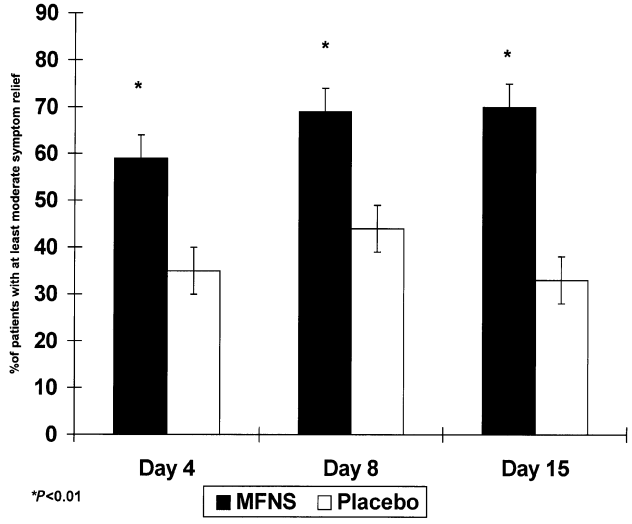

Figure 2. Patients' assessments of at least moderate symptom relief on days 4, 8, and 15.

Patient evaluations at clinic visits

With regard to response to therapy and overall condition of rhinitis, patients who received MFNS indicated significant improvements from baseline relative to those cited by patients who received placebo. Significant relief of symptoms ($P<0.01$) occurred by day 4 (the first clinic evaluation) and was maintained through the end of therapy ($P<0.01$). Overall condition was significantly improved by day 8 ($P<0.01$), and this improvement was also maintained through the end of treatment ($P<0.01$). On day 4, 59% of MFNS-treated patients experienced at least moderate symptom relief, compared with 36% of patients who received placebo. On day 15, the respective values were 72% and 34% (Fig. 2).

Physicians' evaluations at clinic visits

Physicians' assessments also indicated significant superiority of MFNS over placebo. On day 4, total nasal symptom severity was reduced by 34% for MFNS-treated patients and by 16% for those who received placebo ($P<0.01$). The respective decreases were 44% *vs* 28% on day 8 ($P<0.01$) and 43% *vs* 27% at end point ($P<0.01$).

Evaluations of total symptom severity indicated a 32% reduction from baseline for MFNS patients by day 4 compared with 14% for those who received placebo ($P<0.01$). By the end of treatment, the MFNS patients achieved a 41% reduction in total symptom severity, compared with 26% for the placebo group ($P<0.01$).

Physicians' evaluations of overall response to treatment indicated superiority of MFNS over placebo by day 4 (the first evaluation after the initiation of therapy) ($P<0.01$) and through the end of treatment ($P<0.01$). By day 4, 59% of the patients who received MFNS and 37% of those given placebo were rated as having at least moderate relief from rhinitis symptoms. By day 15, these values were 72% and 35%, respectively (Fig. 3). Mean percent change in nasal symptoms showed that MFNS was significantly more effective than placebo ($P<0.02$) at all time points except for stuffiness and itching at end point (Table 2).

Physicians' evaluations of the overall condition of allergic rhinitis also indicated superiority of MFNS over placebo by day 8 ($P=0.02$), which was maintained through the end of treatment ($P<0.01$).

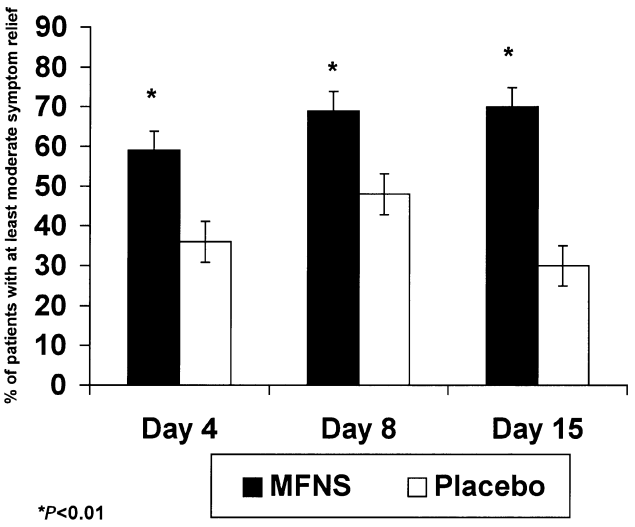

Figure 3. Physicians' evaluation of percentages of patients having at least moderate relief from rhinitis symptoms on days 4, 8, and 15.

Safety

Adverse events considered at least possibly related to treatment occurred in 17% of placebo patients and 12% of those given MFNS. The most common events were headache, epistaxis, nasal burning, and pharyngitis (Table 3). In patients treated with MFNS, no adverse events were rated as severe. No clinically relevant changes in laboratory values or vital signs were noted in any patients.

Discussion

The results of this study demonstrate that MFNS has a rapid onset of action, with approximately one-third of patients experiencing clinically significant symptom relief by 12 h after the first dose and about two-thirds achieving such relief by 72 h. These results provide clinically meaningful data about the onset of symptom relief of allergic rhinitis (prospectively determined) by a corticosteroid nasal spray in a clinically relevant setting.

Other studies have provided information about the onset of action of corticosteroids used to treat allergic rhinitis, but these reports all have limitations. For example, Sim et al. (12) reported that beclomethasone dipropionate (BDP) nasal spray produced significant symptom relief by 3 days after the start of treatment; however, the criteria for clinically significant relief were not prospectively defined. Total symptom severity scores, used to define onset of action, were only abut 25% lower for BDP patients than those for placebo patients at 3 days after the start of treatment. Settipane et al. (13) reported that patients treated with triamcinolone acetonide experienced significant improvement in nasal symptoms after seasonal allergic rhinitis within 12–16 h after the first dose. Significant symptom relief, however, was defined statistically by the change in an index that included nasal stuffiness, discharge, and sneezing rather than by a predefined clinical threshold. In another study using triamcinolone acetonide, Day et al. (5) reported a 25% or greater reduction in nasal congestion from baseline 10 h after initiation of treatment. Patients in this trial, however, received twice the recommended starting dose of this corticosteroid, were primed with allergen, and were studied in an environmental exposure unit. Furthermore, significant symptom relief was defined statistically rather than clinically.

Table 2. Mean percent improvement from baseline in individual nasal symptoms

		Mean percent improvement from baseline		
Symptom	**Evaluation**	**MFNS**	**Placebo**	*P* value[c]
Nasal discharge	Day 4[a]	34%	15%	<0.01
	End point[b]	45%	22%	<0.01
Nasal stuffiness	Day 4	27%	13%	<0.01
	End point	34%	23%	0.07
Sneezing	Day 4	32%	13%	<0.01
	End point	46%	28%	0.02
Nasal itching	Day 4	36%	21%	0.01
	End point	44%	31%	0.06

[a]For each patient, percent improvement was calculated as difference between baseline and post-treatment scores divided by baseline score, multiplied by 100.
[b]Day 4: first office evaluation. End point: last valid visit for each patient except for day 15, for which physician-evaluated scores are not available.
[c]Analysis of variance model was used for comparisons of treatment groups.

Table 3. Treatment-related adverse events

	No. of patients*	
	MFNS (*n*= 101)	**Placebo** (*n*= 99)
Any adverse event	12 (12)	17 (17)
Headache	3 (3)	1 (1)
Epistaxis	1 (1)	3 (3)
Nasal burning	3 (3)	3 (3)
Pharyngitis	3 (3)	3 (3)
Nausea	1 (1)	2 (2)
Sneezing	0	2 (2)

*Number of patients reporting specified adverse event at least once during study. Some patients reported more than one adverse event.

We can only speculate as to why MFNS has a rapid onset of action. First, mometasone furoate is a corticosteroid with high potency, shown to be at least 10 times more efficacious than beclomethasone dipropionate in inhibiting the synthesis and release of proinflammatory mediators such as interleukins-1, -5, and -6, and tumor necrosis factor-alpha (7). This high topical potency may promote a more rapid onset of activity. Second, the rapid onset of action with MFNS may occur (at least in part) because of formation of heterologous complexes with transcription factors for proinflammatory molecules, thereby blocking the activity of anti-inflammatory effects (14). These effects can occur more rapidly than effects of the steroid on gene transcription and protein synthesis. In allergic rhinitis studies, a pronounced placebo effect is commonly seen, particularly when the placebo is a liquid vehicle suspension which has beneficial effects on the nasal mucosa. In this study, the placebo effect was more evident in the comparison of nasal symptom reduction than in the proportion of patients experiencing at least moderate symptom relief. This suggests that symptom relief may be a more sensitive means of assessing the efficacy of therapy.

In summary, MFNS was found to have a rapid onset of action, with clinically significant (at least moderate) symptom relief within 12 h. The efficacy and tolerability of this agent support its first-line use for the treatment of patients with seasonal allergic rhinitis.

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