

A dose-ranging study of mometasone furoate aqueous nasal spray in children with seasonal allergic rhinitis

Eli O. Meltzer, MD,^a William E. Berger, MD,^b Robert B. Berkowitz, MD,^c Edwin A. Bronsky, MD,^d Donald J. Dvorin, MD,^e Albert F. Finn, MD,^f Stanley P. Galant, MD,^g Jay Grossman, MD,^h Frank C. Hampel, MD,ⁱ Paul H. Ratner, MD,^j Michael E. Ruff, MD,^k Eric J. Schenkel, MD,^l Allen T. Segal, MD,^m Nathan Segall, MD,ⁿ George E. Stewart II, MD,^o Ita Tripathy, MD,^p David P. Skoner, MD,^q Robert Anolik, MD,^r Robert J. Dockhorn, MD,^s Julius van Bavel, MD,^t Barbara Mesarina-Wicki, MD,^u and Keith B. Nolop, MD^u San Diego, Mission Viejo, and Orange, Calif; Atlanta, Ga, Salt Lake City, Utah, Forked River and Kenilworth, NJ, Charleston, SC, Tucson, Ariz, New Braunfels, San Antonio, and Dallas, Tex, Easton, Pittsburgh, and Philadelphia, Pa, Ocala, Fla, and Rolla, Mo

Background: The efficacy and safety of mometasone furoate aqueous nasal spray (MFNS; Nasonex) 200 µg once daily for the treatment and prophylaxis of seasonal allergic rhinitis (SAR) and treatment of perennial rhinitis have been demonstrated in adults. However, the dose response of MFNS in pediatric patients has not yet been characterized.

Objective: This study was conducted to determine the dose-response relationship of 3 different doses of MFNS in a pediatric population.

Methods: This was a multicenter, double-blind, active- and placebo-controlled study of 679 children 6 to 11 years of age with histories of SAR and documented positive skin test responses. Patients were randomized to one of the following treatment groups for 4 weeks: MFNS 25 µg once daily, MFNS 100 µg once daily, MFNS 200 µg once daily, beclomethasone dipropionate 84 µg twice daily (168 µg/day), or placebo. Physician evaluations were performed at days 4, 8, 15, and 29, and patient evaluations were analyzed for days 1 to 15 and 16 to 29.

Results: The mean reduction from baseline in physician-evaluated total nasal symptom scores at day 8 (the primary efficacy variable) was significantly greater in the MFNS and beclomethasone dipropionate groups than in the placebo group

($P \leq .02$). No significant differences were observed among the 3 MFNS groups. However, as treatment continued, symptoms in patients treated with MFNS 100 or 200 µg once daily continued to improve, whereas those treated with MFNS 25 µg once daily demonstrated little further improvement. By day 29, MFNS 100 and 200 µg once daily both were significantly more effective than MFNS 25 µg once daily in relieving symptoms of SAR, but MFNS 200 µg provided no additional benefit over MFNS 100 µg. All doses of MFNS were well tolerated, and cosyntropin stimulation tests performed before and after treatment found no evidence of hypothalamic-pituitary-adrenal axis suppression.

Conclusion: These results indicate that the most appropriate therapeutic dosage of MFNS in the treatment of SAR in children 6 to 11 years of age is 100 µg once daily. In addition, MFNS at doses up to 200 µg once daily for 4 weeks was well tolerated and had no detectable effects on hypothalamic-pituitary-adrenal axis function. (*J Allergy Clin Immunol* 1999;104:107-14.)

Key words: Seasonal allergic rhinitis, pediatrics, mometasone furoate

Seasonal allergic rhinitis (SAR) is a common childhood disorder, with an estimated prevalence ranging from 10% to 40%.^{1,2} Proper diagnosis and treatment of childhood allergic rhinitis is important, because the disease may not only cause symptomatic discomfort but also may predispose to other conditions, such as recurrent otitis media and sinusitis, and contribute to increased school absenteeism and impaired performance.³⁻⁶

Although intranasal glucocorticoids are widely accepted as first-line therapy for adults with SAR, some physicians are reluctant to prescribe these agents for children because of concerns about systemic adverse events.⁶ The need for potent intranasal glucocorticoids that have virtually no systemic activity is especially evident in pediatric patients, in whom therapeutic options for allergic rhinitis have historically been more limited than for adults.

Mometasone furoate aqueous nasal spray (MFNS) (Nasonex; Schering-Plough, Inc) is a once daily intranasal glucocorticoid that has been extensively studied in adults with allergic rhinitis.⁷⁻¹¹ A highly potent,

From ^aAllergy and Asthma Medical Group and Research Center, San Diego; ^bprivate practice, Mission Viejo; ^cAtlanta Allergy & Immunology Research Foundation, Atlanta; ^dIntermountain Clinical Research, Salt Lake City; ^eprivate practice, Forked River; ^fAllergy & Asthma Centers of Charleston, Charleston; ^gprivate practice, Orange; ^hVIVRA Research Partners, Tucson; ⁱprivate practice, New Braunfels; ^jSylvana Research, San Antonio; ^kDallas Allergy & Asthma Center, Dallas; ^lprivate practice, Easton; ^mprivate practice, Dallas; ⁿprivate practice, Atlanta; ^oAllergy & Asthma Care of Florida, Ocala; ^pClinical Research of the Ozarks, Inc, Rolla; ^qChildren's Hospital of Pittsburgh, Pittsburgh; ^rAllergy & Asthma Specialists, PC, Philadelphia; ^sInternational Medical Technical Consultants, Inc, Lenexa; ^tprivate practice, Austin; ^uSchering-Plough Research Institute, Kenilworth.

Supported by Schering-Plough Research Institute.

Received for publication June 29, 1998; revised Mar 12, 1999; accepted for publication Mar 12, 1999.

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

Copyright © 1999 by Mosby, Inc.

0091-6749/99 \$8.00 + 0 1/1/98640

Abbreviations used

BDP:	Beclomethasone dipropionate
HPA:	Hypothalamic-pituitary-adrenal
MFNS:	Mometasone furoate aqueous nasal spray
SAR:	Seasonal allergic rhinitis

synthetic 17-heterocyclic glucocorticoid, mometasone furoate is virtually undetectable in plasma after oral or intranasal administration to adults, with an absolute bioavailability of 0.1% or less in healthy volunteers.¹² In a separate study of 48 patients with allergic rhinitis who were 6 to 12 years of age, plasma concentrations of MFNS were too low to be quantified in 99% of post-treatment samples (<50 pg/mL). Therefore the bioavailability of MFNS in these patients was too low to be calculated.¹³

Consistent with its negligible bioavailability, MFNS was found to have no detectable effects on the hypothalamic-pituitary-adrenal (HPA) axis in adults, even at up to 20 times the standard clinical intranasal dose of 200 µg once daily.¹⁴ Clinical trials in adults also have demonstrated the efficacy and tolerability of MFNS in the prophylaxis and treatment of SAR and the treatment of perennial rhinitis.⁷⁻¹¹

On the basis of its excellent efficacy and systemic safety in adults, a clinical research program was undertaken to evaluate the tolerability and efficacy of MFNS in children with SAR. The results of phase-I studies demonstrated that administration of MFNS doses of up to 200 µg once daily was well tolerated in children as young as 3 years of age and resulted in no detectable HPA-axis suppression after 14 days of treatment.¹³

The primary objective of this study was to characterize the dose-response relationship among doses of MFNS ranging from 25 to 200 µg once daily in patients with SAR who were 6 to 11 years of age. The 4-week study also sought to further characterize the local and systemic safety profile of MFNS in these pediatric patients.

METHODS

This was a phase-II, randomized, double-blind, active- and placebo-controlled, parallel-group study of pediatric patients with SAR conducted during the spring of 1996 at 20 centers in the US. All patients were required to have a history of SAR and to be symptomatic during that season. Patients were also required to have a positive response to skin testing for an aeroallergen prevalent during that season, documented by a positive response to either a skin prick test (wheal diameter ≥3 mm larger than that induced by the diluent control) or intradermal testing (≥7 mm larger than that induced by the diluent control). In addition, patients were free from any clinically significant disease other than SAR and were clinically symptomatic at both the screening and baseline visits; female patients were premenarchal.

A washout period was required before screening for any patient who was using intranasal, ocular, oral, inhaled, or systemic medications for rhinitis symptoms. Prescreening medication washout periods were as follows: 12 to 48 hours for short-acting antihistamines

(eg, chlorpheniramine); topical nasal, oral, or ocular decongestants; or topical anti-inflammatory drugs, immunotherapy, and nasal saline; 4 to 7 days for long-acting antihistamines (eg, loratadine, cetirizine, levocabastine, ebastine, and hydroxyzine), nasal atropine, and ipratropium bromide; 2 weeks for nasal cromolyn sodium or nedocromil, nasal or ocular corticosteroids, ketotifen, azelastine, and systemic antibiotics (unless receiving a stable dose); 1 month for oral, inhaled, intravenous, or rectal corticosteroids and high-potency dermatologic corticosteroids (midstrength, potent, or superpotent); and 3 months for intramuscular or intraarticular corticosteroids and astemizole. The use of these medications, as well as nasal saline treatments, was prohibited during the study. Both the study protocol and the informed consent form were approved by a central institutional review board (WIRB, Olympia, Wash) and local institutional review boards when required. All patients and their parents or legal guardians gave written informed consent.

The patients or their guardians filled out a complete medical history and were given a thorough physical examination with vital signs, 12-lead electrocardiography, and clinical laboratory determinations (complete blood cell count, blood chemistry, and urinalysis) at the screening visit and at the completion of the study. In addition, HPA-axis function was evaluated in the patients at 4 study centers at the screening and final visits, with a 30-minute cosyntropin (Cortrosyn; Organon, Inc, West Orange, NJ) stimulation test.

Between the screening and baseline visits, the patients participated in a 2- to 7-day diary run-in phase, during which they recorded SAR symptoms, adverse events, and the use of any medications. No active treatments were administered during the run-in phase; however, the patients were provided with chlorpheniramine maleate syrup as rescue medication for intolerable symptoms. A 4-point scale (0, none; 1, mild; 2, moderate; 3, severe) was used to evaluate the nasal signs and symptoms of rhinorrhea, nasal stuffiness or congestion, nasal itching, and sneezing and the nonnasal symptoms of eye itching, eye tearing, eye redness, and itching of the ears and/or palate. All patients were required to have a total nasal symptom score of 6 or greater (maximum of 12), with a score for nasal congestion of at least 2 (maximum of 3) at both screening and baseline to be included in the study.

At the baseline visit (day 1), the patients were randomized in a 1:1:1:1:1 ratio to 1 of 5 treatment groups: MFNS 25, 100, or 200 µg once daily; beclomethasone dipropionate (BDP) 84 µg twice daily in the morning and evening (168 µg/day); or placebo twice daily. The concentrations of the MFNS preparations were 12.5, 50, and 100 µg/spray; the concentration of the BDP preparation was 42 µg/spray. To maintain the double-blind study design, the patients in the MFNS groups were provided placebo vehicle for the evening dose. The total duration of treatment was 4 weeks. Chlorpheniramine maleate syrup was available throughout the study as rescue medication for intolerable rhinitis symptoms.

Daily pollen counts were performed at each study location to ensure that the patients were exposed to a relevant allergen during the study. Patients and their parents or guardians recorded nasal and nonnasal symptom scores and any adverse events in diaries twice daily. For each subject, the daily scores were averaged over all nonmissing days for days 1 to 15 and days 16 to 29. These values were used to calculate the mean values over the time intervals. Patients returned to the study centers for physician evaluations on days 4, 8, 15, and 29. The physicians scored the nasal and nonnasal symptoms over the past 24 hours, the overall condition of SAR since the previous visit, and the response to therapy compared with baseline. The changes in the scores were determined for the evaluation time point compared with baseline, and a percent reduction in score was calculated.

Symptoms were rated according to the following 5-point scale: 1, complete relief (virtually no symptoms present); 2, marked relief (symptoms are greatly improved and, although present, are scarce-

ly troublesome); 3, moderate relief (symptoms are present and may be troublesome but are noticeably improved); 4, slight relief (symptoms are present, and only minimal improvement has been obtained); 5, treatment failure (no relief; symptoms are unchanged or worse than at baseline).

Patients who discontinued treatment were included in the intent-to-treat population of all randomized subjects. An "endpoint" visit also was derived for each patient to account for those who dropped out. Endpoint was defined as the last visit for which the subject had nonmissing data. For analyses based on evaluable subjects, the endpoint visit was the subject's last valid visit.

For those patients in whom HPA-axis function was evaluated (n = 130), blood samples were collected at the screening visit and before the morning dose on day 29 to determine morning plasma cortisol levels. Additional blood samples were obtained 30 minutes after an intravenous injection of 0.25 mg of cosyntropin to evaluate the response to adrenal stimulation.

At screening, each patient was required to have a normal cortisol level of at least 5 µg/100 mL. Thirty minutes after cosyntropin stimulation, the cortisol level was expected to increase by at least 7 µg/100 mL to a value of at least 18 µg/100 mL. Cortisol levels that increased to less than 18 µg/100 mL were considered indicative of HPA-axis suppression.

Statistical analysis

The study was designed to have a power of 90% to detect a difference between MFNS and placebo of at least 1 unit with respect to the change from baseline in the total nasal symptom score on day 8. This required 100 subjects per treatment group using a 2-sided test with 5% significance level and assuming a pooled standard deviation of 2.27 units. Because of differential rates of accrual at several sites, some sites accrued subjects faster than others. Consequently, the total number of subjects in the study (679) was higher than originally planned.

The primary efficacy variable was the mean change from baseline in the physicians' evaluation of total nasal symptom score at day 8 in all randomized subjects (the intent-to-treat population). A linear contrast of the treatment means, obtained from a 2-way ANOVA that extracted sources of variation as a result of treatment, center, and treatment-by-center interaction was used to test for increasing response with increasing MFNS dose. To perform this test, the coefficients for the 4 treatment groups (MFNS 25, 100, and 200 µg and placebo) were -3, -1, 1, and 3.

All pairwise treatment comparisons then were performed based on the least-squares means from the ANOVA by using an individual 5% (2-sided) significance level for each comparison. Because the linear contrast was identified as the primary test for assessing the effectiveness of MFNS, the individual treatment comparisons were carried out with no adjustment for multiple comparisons.

In addition to the analysis of the day-8 visit, all 10 pairwise comparisons among the 5 treatment groups were made with respect to the change from baseline in total nasal symptom scores for each scheduled visit (including endpoint) by using the same 2-way ANOVA. Finally, the analysis of the primary efficacy variable was repeated for evaluable subjects (pooled across all centers) by using the identical contrast test based on the ANOVA.

The same 2-way ANOVA based on the intent-to-treat population was used for the evaluation of the composite and individual symptom scores, for evaluations of overall condition of SAR and response to therapy, and for evaluations of the cosyntropin stimulation tests. The following variables were analyzed for the cosyntropin stimulation tests: prestimulation values, poststimulation values, the difference between the poststimulation and prestimulation values, and the change from screening in the difference between poststimulation and prestimulation values.

TABLE I. Baseline demographic characteristics of the intent-to-treat population

	MFNS 25 µg QD (n = 137)	MFNS 100 µg QD (n = 135)	MFNS 200 µg QD (n = 133)	BDP 84 µg BID (n = 138)	Placebo (n = 136)
Age (y)					
Mean	9	9	9	9	9
(range)	(6-11)	(6-11)	(6-12)	(5-11)	(6-11)
Sex					
M	85	84	79	87	84
F	52	51	54	51	52
Race					
White	114	111	112	119	113
Black	11	11	8	8	11
Other	12	13	13	11	12

QD, Once daily; BID, twice daily.

RESULTS

Study population

A total of 679 pediatric patients of either sex with at least a 1-year history of SAR were enrolled in the study; the baseline demographics of the study population are shown in Table I. The patients had a mean age of 9 years, most were white, and there was a preponderance of males in each group. The protocol was to enroll children 6 to 11 years of age. However, one 5-year-old and one 12-year-old child were also enrolled. Although these children were in violation of the entry criteria, they are included in the data because this error was not discovered until after the patients had been randomized to treatment, thus becoming part of the intent-to-treat population. Most patients had a history of SAR for 5 or 6 years, and were currently symptomatic for about 30 days before treatment. Slightly more than 70% also had a history of perennial allergic rhinitis, and about 40% had a history of asthma.

Thirty-three patients (5%) discontinued treatment before the completion of the study; 14 of these patients (2%) discontinued as a result of adverse events, with a comparable distribution among the 4 active treatment groups and the placebo group. There were only 4 treatment failures (<1%): 1 in the MFNS 25 µg once daily group, 2 in the BDP 84 µg twice daily group, and 1 in the placebo group. Treatment failure was defined by the patient (in cooperation with the clinician) who determined that the symptoms were too great to continue in the study to its proposed completion, requiring early withdrawal of the patient from the study.

Efficacy

According to physician evaluations of total nasal symptom scores at day 8 (the primary efficacy variable), all active treatments were significantly more effective than placebo ($P \leq .02$), and there were no significant differences among active treatments (Fig 1). Similar results were seen at day 4. During the last 3 weeks of the study, physician ratings of total nasal symptoms for patients in

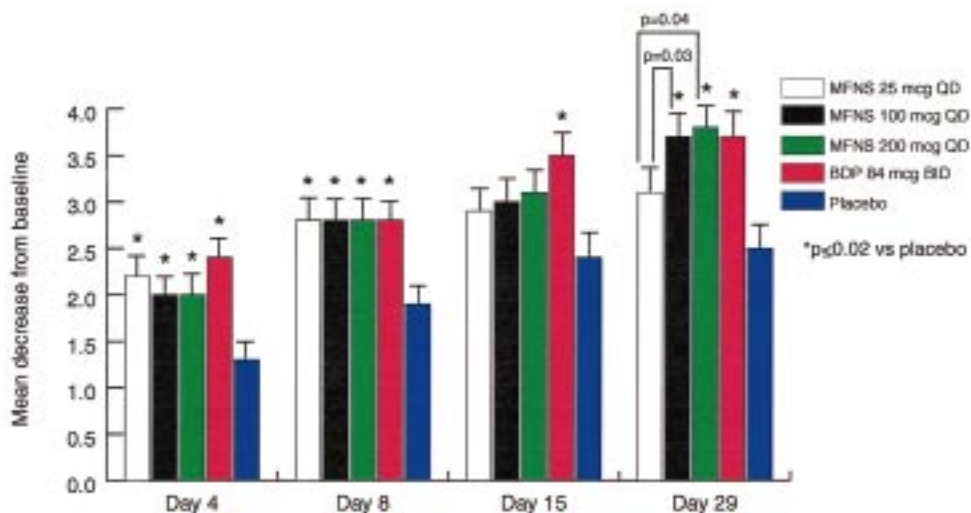


FIG 1. Reduction in physician-evaluated total nasal symptom scores in children with SAR during treatment with MFNS, BDP, or placebo.

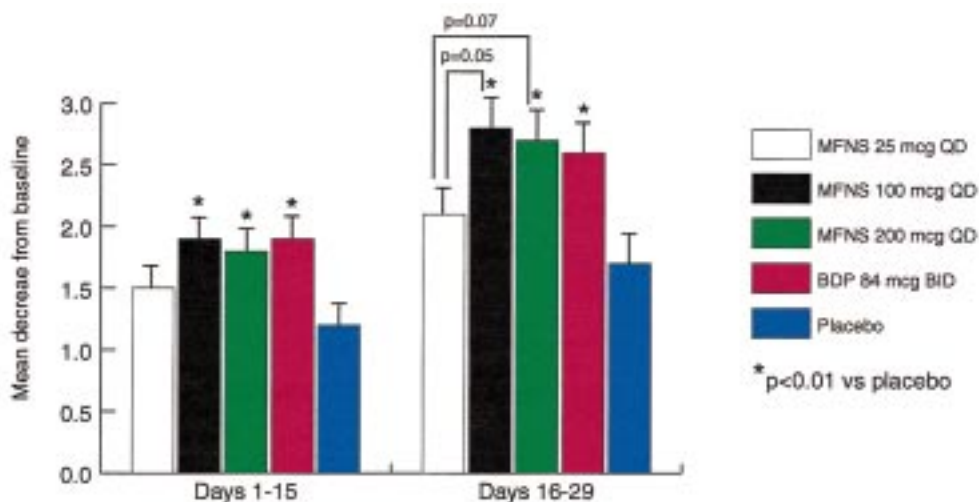


FIG 2. Reduction in total nasal symptom scores from patient diaries of children with SAR during treatment with MFNS, BDP, or placebo.

the MFNS 100 and 200 μg once daily and BDP 84 μg twice daily groups continued to improve, but little improvement was noted for the patients treated with MFNS 25 μg once daily or placebo. There were not any significant differences in the reduction of total nasal symptom scores at days 15 and 29 between the MFNS 25 μg once daily and placebo groups or between the BDP group and any MFNS group.

By day 29, differences among the MFNS treatment groups in relieving nasal symptoms were evident. MFNS 100 μg once daily was significantly more effective than MFNS 25 μg once daily (46% vs 38%, $P = .03$), as was MFNS 200 μg once daily (47% vs 38%, $P = .04$). However, MFNS 200 μg once daily offered no additional benefit over MFNS 100 μg once daily at any time point throughout the study.

The analysis of the patient-evaluated total nasal symptom scores for days 1 to 15 and days 16 to 29 showed trends similar to those observed for the physician-evaluated scores (Fig 2). The mean reductions from baseline for the MFNS 100 and 200 μg once daily groups and for the BDP 84 μg twice daily group were significantly greater ($P < .01$) than those for the placebo group for days 1 to 15. There were not any significant differences ($P > .05$) between the MFNS 25 μg once daily group and the placebo group or between any of the MFNS groups and the BDP group during this period. However, during days 16 to 29, MFNS 100 μg once daily was significantly more effective than MFNS 25 μg once daily (38% vs 32%, $P = .05$). There was no additional benefit of MFNS 200 μg once daily over MFNS 100 μg once daily during either of the subject-evaluated time periods.

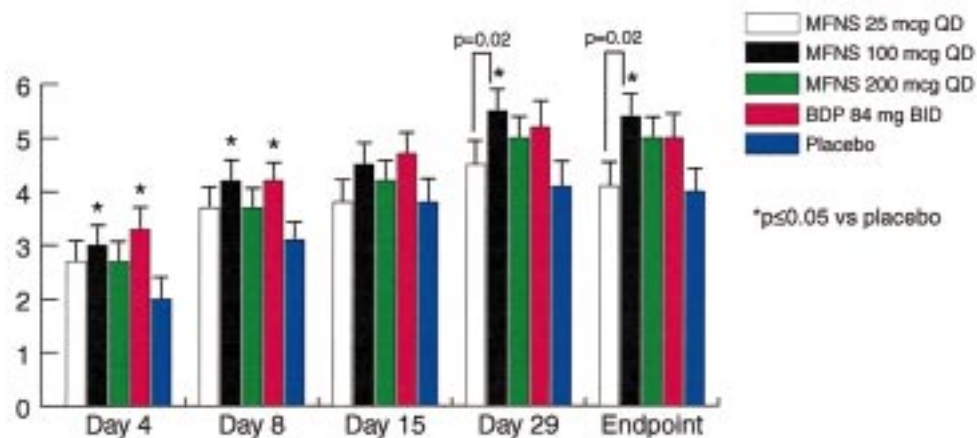


FIG 3. Change from baseline in physician-evaluated total symptom scores for the intent-to-treat population.

Physician-evaluated total symptom scores (nasal plus nonnasal) were also similar to the physician-evaluated total nasal scores (Fig 3). Mean reductions were consistently greater in the MFNS groups (22% to 44%) and the BDP group (29% to 43%) than in the placebo group (15% to 32%). MFNS 100 μ g once daily was significantly more effective than placebo in reducing total symptoms at days 4, 8, and 29 and at endpoint ($P \leq .04$). BDP 84 μ g twice daily was significantly more effective than placebo only at days 4 and 8 ($P \leq .05$). There were not any significant differences in the reduction of total symptoms between either MFNS 25 or 200 μ g once daily and placebo or between any of the MFNS treatment groups and the BDP group. At day 29, MFNS 100 μ g once daily was more effective than MFNS 25 μ g once daily (44% vs 36%, $P = .02$), whereas MFNS 200 μ g once daily offered no additional benefit over MFNS 100 μ g once daily.

Similarly, mean reductions in patient-evaluated total symptom scores were significantly greater for the MFNS 100 μ g once daily group than the placebo group for days 16 to 29. No other significant differences were observed between the MFNS dose groups or the BDP group and placebo or among the MFNS dose groups.

Both physician- and patient-evaluated scores for individual symptoms were also analyzed, and the results were similar to those observed with the total nasal and total symptom scores. In general, MFNS 25 μ g once daily was effective at the beginning of treatment, but the improvement in symptoms was less consistent over time than the improvement seen with the higher MFNS doses. At the end of the study, MFNS 100 and 200 μ g once daily were more effective than placebo in reducing individual symptoms. Except for the reduction of nasal discharge by MFNS 100 μ g ($P = .11$), these differences were statistically significant ($P < .05$) for all physician-rated scores of nasal congestion, nasal discharge, nasal itching, and sneezing. Results from patient ratings were similar. MFNS 200 μ g provided no additional benefits over MFNS 100 μ g.

Mean scores for the physicians' and the patients' evaluations of the overall response to treatment indicated that all active treatments provided greater relief than placebo from SAR symptoms throughout the study. Significant differences ($P \leq .04$) between the active treatments and placebo were observed at several time points for the physician evaluations. There were not any significant differences between BDP 84 μ g twice daily and any of the MFNS once daily doses or among the 3 MFNS dose groups. At endpoint (the patient's final visit), complete, marked, or moderate relief was noted for 69%, 71%, and 74% of the patients treated with MFNS 25, 100, and 200 μ g once daily, respectively; such relief was noted by 70% of patients treated with BDP 84 μ g twice daily and 57% of patients given placebo. Similar results were seen in the patients' evaluation of overall response.

Overall, 61% of the patients used rescue medication at least once during the study; the incidence ranged from 61% to 64% in the 3 MFNS groups, 52% in the BDP group, and 66% in the placebo group. There was no overall significant difference among the 5 treatment groups in their use of rescue medication.

Safety and tolerability

All active treatments were well tolerated locally, and the overall incidence of treatment-related adverse events was similar among the 5 treatment groups (Table II). The most frequently reported treatment-related adverse events were headache and epistaxis, which occurred at similar incidences among the 5 treatment groups. The incidence of headache ranged from 3% in the MFNS 25 and 100 μ g groups to 7% in the MFNS 200 μ g group. Epistaxis/blood in nasal discharge occurred at incidences ranging from 2% in the MFNS 200 μ g group to 7% in the placebo and MFNS 25 μ g groups. In the majority of patients, epistaxis was mild in severity, intermittent, and of short duration.

Among the other frequently reported treatment-related adverse events were sneezing and pharyngitis, which occurred with similar frequency among the 5 treatment

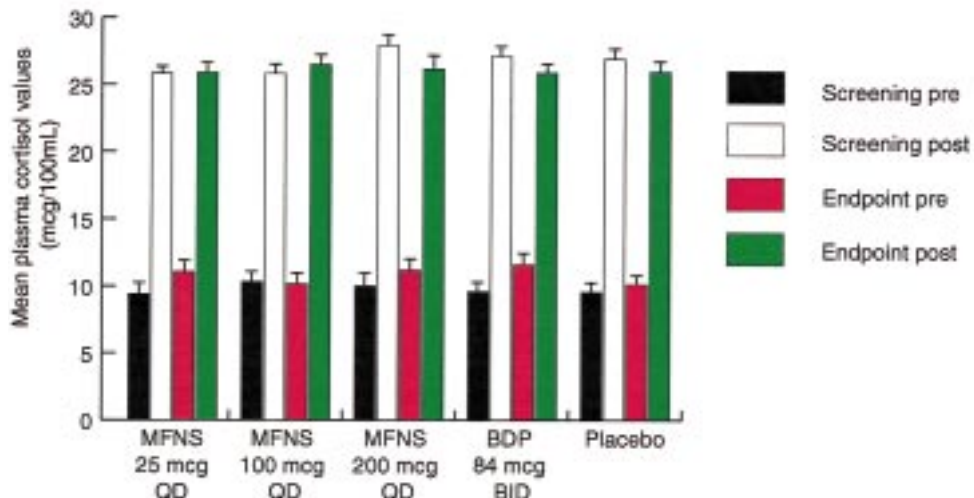


FIG 4. Mean plasma cortisol values measured before and after cosyntropin stimulation at screening and at the endpoint visit after treatment with MFNS, BDP, or placebo in children with SAR. Baseline cortisol values were required to be at least 5 $\mu\text{g}/100\text{ mL}$. All patients had a normal response to cosyntropin stimulation (both before and after treatment), which included an increase over baseline values of at least 7 $\mu\text{g}/100\text{ mL}$ and an absolute value of at least 18 $\mu\text{g}/100\text{ mL}$. There were no significant within-group differences between mean screening and endpoint values for the prestimulation or poststimulation cortisol levels.

TABLE II. Incidence of most frequently reported treatment-related adverse events*

	MFNS 25 μg QD (n = 137)	MFNS 100 μg QD (n = 135)	MFNS 200 μg QD (n = 133)	BDP 84 μg BID (n = 138)	Placebo (n = 136)
Any adverse event	24 (18%)	27 (20%)	19 (14%)	21 (15%)	31 (23%)
Headache	4 (3%)	4 (3%)	9 (7%)	8 (6%)	8 (6%)
Epistaxis	10 (7%)	8 (6%)	3 (2%)	6 (4%)	9 (7%)
Pharyngitis	2 (1%)	1 (1%)	2 (2%)	4 (3%)	3 (2%)
Sneezing	6 (4%)	4 (3%)	0	1 (1%)	6 (4%)
Coughing	1 (1%)	2 (1%)	2 (2%)	2 (1%)	1 (1%)
Nasal irritation	0	3 (2%)	0	0	0

*Adverse events reported for at least 2% of patients in any treatment group and considered possibly, probably, or definitely related to treatment.
QD, Once daily; BID, twice daily.

groups and at incidences of 4% or less. Coughing and nasal irritation occurred at incidences of 2% or less.

Most adverse events were mild or moderate in severity, and the incidence of severe treatment-related adverse events was low: 1% in each of the 3 MFNS groups, 2% in the BDP group, and 3% in the placebo group. Severe treatment-related adverse events were as follows: headache and sneezing in MFNS-treated patients; headache, viral infection, and nasal burning in BDP-treated patients; and epistaxis, rhinitis, sneezing, and conjunctivitis in placebo-treated patients. No patient experienced more than one severe treatment-related adverse event. A total of 14 patients discontinued treatment because of adverse events, primarily a concomitant illness considered unrelated to the study drug. No treatment-related serious adverse events occurred, and there were no adverse events related to the cosyntropin stimulation tests.

No clinically meaningful changes from baseline were

observed in the results of clinical laboratory tests for any patient in any treatment group. Similarly, there were no clinically relevant changes in vital signs or electrocardiogram results after 4 weeks of treatment, and physical examinations were unremarkable, except for the decrease in rhinitis symptoms as noted above.

All patients for whom HPA-axis function was assessed (25 to 27 patients per group) had a normal response to cosyntropin stimulation after 4 weeks of treatment. Mean screening prestimulation values for morning plasma cortisol were comparable among the 5 treatment groups and ranged from 9.38 to 10.28 $\mu\text{g}/100\text{ mL}$; after cosyntropin stimulation, mean plasma cortisol levels increased by 15.53 to 17.90 $\mu\text{g}/100\text{ mL}$ to mean values ranging from 25.82 to 27.90 $\mu\text{g}/100\text{ mL}$ (Fig 4).

After 4 weeks of treatment, mean prestimulation plasma cortisol levels ranged from 10.13 to 11.59 $\mu\text{g}/100\text{ mL}$ and increased by 14.27 to 16.32 $\mu\text{g}/100\text{ mL}$ after cosyntropin stimulation to values ranging from 25.86 to 26.47

$\mu\text{g}/100\text{ mL}$. Neither the prestimulation nor the poststimulation mean values were significantly different at endpoint from screening levels in any treatment group. At endpoint, there was 1 patient in the placebo group, 1 patient in the MFNS 25 μg group, and 1 patient in the MFNS 100 μg group who had prestimulation cortisol values between 4.5 and 5.0 $\mu\text{g}/100\text{ mL}$. No patient in either the MFNS 200 μg or BDP treatment groups had an endpoint prestimulation cortisol value that was below 5.0 $\mu\text{g}/100\text{ mL}$.

DISCUSSION

These results indicate that MFNS was efficacious and well tolerated in the treatment of SAR in children 6 to 11 years of age. On the basis of the tabulation of symptom scores and assessments of overall response to therapy with MFNS doses ranging from 25 to 200 μg once daily, 100 μg once daily appears to be the most appropriate therapeutic dosage. The MFNS dose of 100 μg is consistent with the practice of treating children with half of the recommended adult dose (MFNS 200 μg once daily). It is also consistent with pediatric studies of fluticasone propionate, which demonstrated efficacy in SAR at half the adult daily dose.^{15,16}

No differences were observed among the 3 doses of MFNS for the primary efficacy variable (change from baseline in total nasal symptom scores at day 8). However, according to both the physicians' and patients' evaluations of total nasal symptom scores, MFNS 100 and 200 μg once daily provided consistent relief of SAR symptoms throughout the study, whereas MFNS 25 μg once daily was less consistently effective. MFNS 200 μg once daily provided no additional effectiveness compared with the 100- μg dose.

The active comparator in this study, BDP aqueous nasal spray, has documented clinical efficacy in pediatric patients with SAR.^{17,18} In this study once daily MFNS demonstrated comparable efficacy to twice daily BDP in terms of symptomatic relief. In general, there were no important differences between BDP and MFNS in evaluations made by the physicians or patients. Although BDP has been shown to be effective when given once daily in adults, there have been no well-controlled studies of this regimen in children. In addition, the lower bioavailability of MFNS may be particularly meaningful in children with respect to short- and long-term suppression of growth. This potential adverse effect appears to occur with intranasal BDP¹⁹ and may also occur with other intranasal glucocorticoids, particularly when the nasal preparation is added to the total glucocorticoid dose a child may be receiving by other routes for concomitant conditions, such as asthma.

The placebo response rate in this study was relatively high; 57% of placebo-treated patients were judged by physicians to have a complete, marked, or moderate overall response to treatment at endpoint. This result may be due in part to the fact that the placebo preparation was the vehicle spray, which might provide some relief of

rinitis symptoms. Other contributing factors may include underobservation and underreporting of symptoms by children and waning of pollen counts near the end of the allergen season.

All doses of MFNS were well tolerated in this study, and no dose-response relationship was observed in the incidence of adverse effects among the MFNS groups. Headache was the most frequently reported treatment-related adverse event in all treatment groups, including placebo. MFNS and BDP were equally well tolerated, and the incidence and types of adverse events reported with the active treatments were similar to those observed in the placebo group. Epistaxis, nasal irritation, and other local adverse events were usually mild, intermittent, and of short duration. Intranasal steroids usually increase the rate of epistaxis and blood-tinged mucus; therefore the lower incidence of epistaxis in patients receiving higher dosages of MFNS reinforces the excellent tolerability of MFNS in pediatric patients.

Cosyntropin stimulation testing performed at the screening and final visits in 130 of these pediatric patients indicated no suppression of HPA-axis function after 4 weeks of MFNS treatment. These results are consistent with previous reports demonstrating that MFNS had no detectable effects on the HPA axis in patients as young as 3 years of age treated with MFNS 200 μg for up to 14 days or in adults who received single doses of MFNS up to 20 times the standard 200 μg clinical dose.^{13,14}

In conclusion, the results of this dose-ranging study indicate that MFNS 100 μg once daily is an appropriate therapeutic regimen for the relief of SAR symptoms in children. MFNS 25, 100, or 200 μg once daily provided greater symptomatic relief than placebo and a response comparable with that observed after treatment with BDP 84 μg twice daily. All doses of MFNS were well tolerated, and there was no indication of suppression of HPA-axis function in these children after 4 weeks of treatment. These findings indicate that MFNS 100 μg once daily is safe, effective, and well tolerated for the treatment of SAR in pediatric patients as young as 6 years of age.

REFERENCES

1. Wright AL, Holberg CJ, Martinez FD, et al. Epidemiology of physician-diagnosed allergic rhinitis in childhood. *Pediatrics* 1994;94:895-901.
2. Ricketti AJ. Allergic rhinitis. In: Patterson R, editor. *Allergic diseases: diagnosis and management*. Philadelphia: Lippincott Company; 1985. p. 208.
3. Fireman P. Otitis media and eustachian tube dysfunction: connection to allergic rhinitis. *J Allergy Clin Immunol* 1997;99:S787-97.
4. Spector SL. Overview of comorbid associations of allergic rhinitis. *J Allergy Clin Immunol* 1997;99:S773-80.
5. Sly RM. Allergy and school problems. In: Bierman CW, Pearlman DS, editors. *Allergic disease of infancy, childhood and adolescence*. Philadelphia: WB Saunders Co; 1980. p. 746-50.
6. International Rhinitis Management Working Group. International Consensus report on the diagnosis and management of rhinitis. *Allergy* 1994;49(suppl 19):1-34.
7. Bronsky EA, Aaronson DW, Berkowitz RB, et al. Dose ranging study of mometasone furoate (Nasonex) in seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 1997;79:51-6.
8. Hebert JR, Nolop K, Lutsky B. Once daily mometasone furoate aqueous

- nasal spray (Nasonex™) in seasonal allergic rhinitis: an active- and placebo-controlled study. *Allergy* 1996;51:569-76.
9. Graft D, Aaronson D, Chervinsky P, et al. A placebo- and active-controlled randomized trial of prophylactic treatment of seasonal allergic rhinitis with mometasone furoate aqueous nasal spray. *J Allergy Clin Immunol* 1996;98:724-31.
 10. Drouin M, Yang WH, Bertrand B, et al. Once daily mometasone furoate aqueous nasal spray is as effective as twice daily beclomethasone dipropionate for perennial allergic rhinitis patients. *Ann Allergy Asthma Immunol* 1996;77:153-60.
 11. Davies RJ, Nelson HS. Once-daily mometasone furoate nasal spray: efficacy and safety of a new intranasal glucocorticoid for allergic rhinitis. *Clin Ther* 1997;19:27-38.
 12. Onrust SV, Lamb HM. Mometasone furoate: a review of its intranasal use in allergic rhinitis. *Drugs* 1998;56:725-45.
 13. Brannan MD, Herron JM, Affrime MB. Safety and tolerability of once-daily mometasone furoate aqueous nasal spray in children. *Clin Ther* 1997;19:1330-9.
 14. Brannan MD, Seiberling M, Cutler DL, et al. Lack of systemic activity with intranasal mometasone furoate [abstract]. *J Allergy Clin Immunol* 1996;97:198.
 15. Boner A, Sette L, Martinati L, Sharma RK, Richards DH. The efficacy and tolerability of fluticasone propionate aqueous nasal spray in children with seasonal allergic rhinitis. *Allergy* 1995;50:498-505.
 16. Fluticasone Propionate Collaborative Pediatric Working Group. Treatment of seasonal allergic rhinitis with once-daily intranasal fluticasone propionate therapy in children. *J Pediatr* 1994;125:628-34.
 17. Prah P, Wilken-Jensen K, Mygind N. Beclomethasone dipropionate in aerosol treatment of hay fever in children. *Arch Dis Child* 1975;50:875-8.
 18. Shore SC, Weinberg EG. Beclomethasone dipropionate aerosol in treatment of perennial allergic rhinitis in children. *Arch Dis Child* 1977;52:486-8.
 19. Rachelefsky GS, Chervinsky P, Meltzer EO, et al. An evaluation of the effects of beclomethasone dipropionate aqueous nasal spray (Vancenase AQ [VNS]) on long-term growth in children [abstract]. *J Allergy Clin Immunol* 1998;101:S236.