

Onset of symptomatic effect of mometasone furoate nasal spray in the treatment of nasal polyposis

Catherine Butkus Small, MD,^a Paul Stryczak, PhD,^c Melvyn Danzig, PhD,^c and Angela Damiano, MD^b

Valhalla, NY, and Kenilworth, NJ

Background: The efficacy of the intranasal corticosteroid mometasone furoate nasal spray (MFNS) for treatment of nasal polyposis was demonstrated in 2 large clinical trials.

Objective: To evaluate the onset of MFNS symptomatic effect, data from the 2 trials were pooled and analyzed to determine the first day subjects experienced significant symptom relief.

Methods: Subjects with nasal polyposis randomized to MFNS 200 µg twice daily or placebo scored symptoms on a 3-point scale (0 = none; 3 = severe) and measured peak nasal inspiratory flow immediately before the morning dose. Onset of symptomatic effect was defined as the first day a statistically significant ($P < .05$) lasting response was observed for MFNS compared with placebo.

Results: A total of 447 subjects with bilateral nasal polyps and clinically significant nasal congestion/obstruction were analyzed. Compared with placebo, MFNS 200 µg twice daily demonstrated statistically significant ($P < .05$) relief of anterior rhinorrhea by day 2 (−10.9% vs +5.7%), nasal congestion by day 3 (−15.1% vs −7.6%), postnasal drip by day 5 (+1.1% vs +4.6%), and sense of smell by day 13 (−9.6% vs −5.6%).

Significant improvement in peak nasal inspiratory flow was seen by day 2 (increase of 6.22 L/min vs 1.48 L/min for placebo; $P = .03$).

Conclusion: Mometasone furoate nasal spray 200 µg twice daily rapidly improves the symptoms of nasal polyposis, leading to lasting relief of most major symptoms within 2 (24 hours after the first dose) to 5 days of initiating therapy. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Nasal polyposis, mometasone furoate, efficacy onset, intranasal corticosteroids, clinical trial

Approximately 4% of the population has nasal polyps.¹ Symptoms include nasal obstruction, nasal congestion, nasal discharge, rhinorrhea, purulence, and postnasal drip.² More than 75% of

Abbreviations used

LS: Least squares

MFNS: Mometasone furoate nasal spray

PNIF: Peak nasal inspiratory flow

patients with nasal polyps also experience impairment or loss of sense of smell.³

The cause of nasal polyps is not completely understood, although they are often associated with asthma, aspirin sensitivity, or cystic fibrosis. Enterotoxins released in the nasal cavity by colonizing bacteria such as *Staphylococcus aureus* may act as superantigens that influence the activity of both immunomodulatory and proinflammatory effector cells.⁴ Nasal polyposis is characterized primarily by eosinophilic inflammation, which initiates an autocrine inflammatory mechanism causing persistent eosinophilia, as well as by increased levels of other inflammatory mediators, such as IL-5, eotaxin, and eosinophilic cationic protein.⁵⁻⁷ In bilateral nasal polyposis, the typical form of the disease in adults, a mixed cellular infiltrate consisting primarily of eosinophils occurs.⁶

Topical intranasal corticosteroids, which inhibit the eosinophil-associated inflammation found with polyposis without affecting the immune response, have been shown in numerous studies to reduce polyp grade (size and extent), improve symptoms, and delay or reduce the need for surgery.^{2,8-17} Intranasal corticosteroids are currently considered the medical treatment of choice for nasal polyposis.¹⁸ In 2 recent, large, multicenter, placebo-controlled studies, mometasone furoate nasal spray (MFNS) demonstrated significant, lasting symptom relief compared with placebo in nasal congestion/obstruction, anterior rhinorrhea, and postnasal drip scores, and significantly improved sense of smell. Peak nasal inspiratory flow rates and quality of life assessment scores also significantly increased with MFNS.^{17,19} In these studies, 200 µg MFNS taken twice daily was superior to a 200-µg/d dose in reducing nasal congestion/obstruction. In addition, a greater percentage of these subjects demonstrated an overall improvement in their symptoms after 4 months.¹⁷ As a result, data on the 200-µg twice-daily dose of MFNS from these trials were pooled and further analyzed to evaluate the onset of the symptomatic effect of MFNS on nasal polyposis.

METHODS

Pooled data from 2 randomized, multinational, double-blind, placebo-controlled, parallel-group 4-month clinical trials conducted between June

From ^athe Division of Infectious Diseases and ^bthe Division of Otolaryngology, New York Medical College, Westchester Medical Center, Valhalla; and ^cthe Schering-Plough Research Institute, Kenilworth.

Supported by a grant from the Schering-Plough Research Institute.

Disclosure of potential conflict of interest: P. Stryczak is employed by Schering-Plough. M. Danzig has consulting arrangements with, owns stock in, and was formerly employed by Schering-Plough. The rest of the authors have declared that they have no conflict of interest.

Received for publication May 23, 2007; revised October 18, 2007; accepted for publication November 12, 2007.

Reprint requests: Catherine Butkus Small, MD, Division of Infectious Diseases, Munger Pavilion Rm 245, Valhalla, NY 10595. E-mail: Catherine_Small@nymc.edu.
0091-6749/\$34.00

© 2008 American Academy of Allergy, Asthma & Immunology
doi:10.1016/j.jaci.2007.11.018

2001 and March 2003 were further analyzed.^{17,19} Subjects were at least 18 years of age, had endoscopically confirmed bilateral nasal polyps, and were required to have clinically significant nasal congestion on each of the last 7 days of a 14-day placebo run-in period. Further inclusion/exclusion criteria have been previously reported.^{17,19} Subjects evaluated their symptoms, including nasal congestion/obstruction, loss of sense of smell, anterior rhinorrhea, and postnasal drip every morning immediately before dosing, using a diary card with a 0 to 3 scale (0 = none; 3 = severe). A lower percentage score correlated with greater symptom improvement. Peak nasal inspiratory flow (PNIF) was measured with a meter, with a higher score indicating greater symptom improvement.

Polyps were graded by size and extent monthly in both nostrils on the following scale: 0 = no polyps; 1 = polyps in middle meatus, not reaching below the inferior border of the middle turbinate; 2 = polyps reaching below the inferior border of the middle turbinate but not the inferior border of the inferior turbinate; and 3 = large polyps reaching to or below the lower border of the inferior turbinate or polyps medial to the middle turbinate.¹⁷

The onset of symptomatic effect of MFNS 200 µg twice daily was the efficacy endpoint, defined as the first day when a statistically significant response ($P < .05$) was observed for MFNS versus placebo over month 1 of the study. If statistical significance for a symptom was not achieved by day 7, the study period was extended until statistical significance was reached. Symptoms were evaluated for as long as 45 days. Differences between treatment groups in changes from baseline (day 1) for each day of the study were assessed by a 2-way ANOVA. Least square (LS) means, pooled SDs, P values, and pairwise comparison P values were obtained from ANOVA with treatment, baseline asthma status, and side effects. Because this was a *post hoc* analysis of data, there were no prospectively defined primary and secondary endpoints.

RESULTS

Data from 447 subjects were analyzed. Of these, 224 received MFNS 200 µg twice daily and 223 received placebo. There were no significant differences in demographic characteristics. Bilateral polyp scores were 4.20 in both groups (Table I). Baseline symptom scores and PNIF scores also did not differ between the groups. A statistically significant improvement was observed for all symptoms except sense of smell at day 7 compared with placebo. This improvement in symptoms continued until day 45, except for sense of smell, which improved significantly until day 44 (Table II).

Anterior rhinorrhea

A statistically significant improvement in LS mean anterior rhinorrhea score was first experienced on day 2 (24 hours after the first dose; -0.18 [95% CI, -0.33 to -0.03] MFNS vs $+0.03$ [5.7%] placebo; Fig 1). The placebo-adjusted treatment effect was -0.21 (95% CI, -0.33 to -0.10 ; $P < .001$). Improvement in anterior rhinorrhea remained significantly greater at day 7 with a decrease of -0.27 (19.5%) for MFNS versus an increase of 0.03 (8.5%) for placebo, a treatment effect of -0.30 (95% CI, -0.43 to -0.19 ; $P < .001$). The maximum treatment effect, defined as the largest decrease in symptom score from baseline, was seen on day 24, with a 37.8% decrease. MFNS-treated subjects continued to improve significantly compared with placebo every day until day 45 ($P < .001$; Fig 1; Table II).

Nasal congestion/obstruction

Least square mean nasal congestion scores improved significantly from baseline in MFNS-treated subjects, with a statistically significant improvement first experienced on day 3 (-0.34 [15.1%] MFNS vs -0.20 [7.6%] placebo). The placebo-

TABLE I. Demographics of 447 subjects with bilateral nasal polyposis

	MFNS 200 µg twice daily (n = 224)	Placebo (n = 223)
Mean age, y (range)	47.8 (18.0-77.0)	49.2 (18.0-81.0)
Age subgroup, n (%)		
18 to <65 y	196 (87.5)	192 (86.1)
>65 y	28 (12.5)	31 (13.9)
Male (%)	63	63
Asthma history, n (%)	45 (20.1)	42 (18.8)
Perennial allergic rhinitis history, n (%)	48 (21.4)	42 (18.8)
Initial bilateral polyp grade scores	4.20	4.20

adjusted treatment effect was -0.14 (95% CI, -0.25 to -0.04 ; $P < .01$). Statistically significant improvement continued to day 7 (-0.52 [21.9%] MFNS vs -0.21 [6.6%] placebo), for a treatment effect of -0.31 (95% CI, -0.44 to -0.19 ; $P < .01$). The maximum treatment effect occurred on day 43, with a 37.7% decrease. Significant improvement in the MFNS-treated group compared with placebo continued until day 45 ($P < .001$; Fig 2; Table II).

Postnasal drip

Mometasone furoate-treated subjects first experienced a statistically significant reduction in postnasal drip compared with placebo on day 5 (-0.18 [1.1%] MFNS vs 0.0 [4.6%] placebo), a treatment effect of -0.18 (95% CI, -0.30 to -0.05 ; $P < .05$; Fig 3). Symptoms continued to improve significantly through day 7 (-0.18 [7.3%] MFNS vs 0.02 [10.1%] placebo), a treatment effect of -0.20 (95% CI, -0.32 to -0.08 ; $P < .05$). The maximum treatment effect occurred on day 42, with a 22.6% decrease. MFNS-treated subjects continued to improve compared with placebo every day until day 45 ($P < .003$; Fig 3; Table II).

Sense of smell

Sense of smell in MFNS-treated subjects improved significantly and remained significantly greater than placebo for the first time on day 13 (-0.22 [9.6%] MFNS vs -0.10 [5.6%] placebo), a treatment effect of -0.12 (95% CI, -0.24 to -0.00 ; $P < .05$). MFNS-treated subjects had a statistically significant improvement in sense of smell compared with placebo on most, but not all, treatment days, until but not including day 45 ($P < .05$). Improvement in symptom scores was significant on days 13 to 31, day 34, and days 38 to 44 (Fig 4; Table II). The maximum treatment effect was reached on day 39, with a 20.9% decrease.

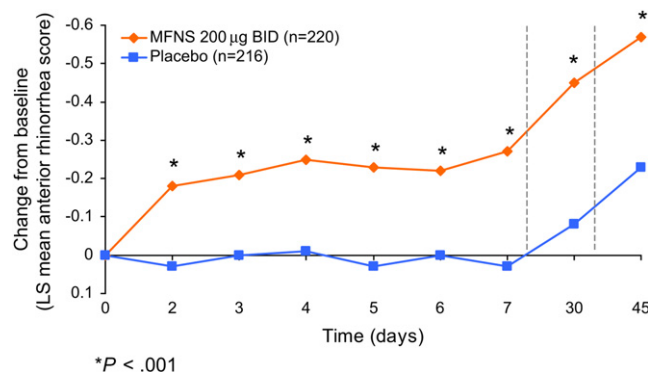
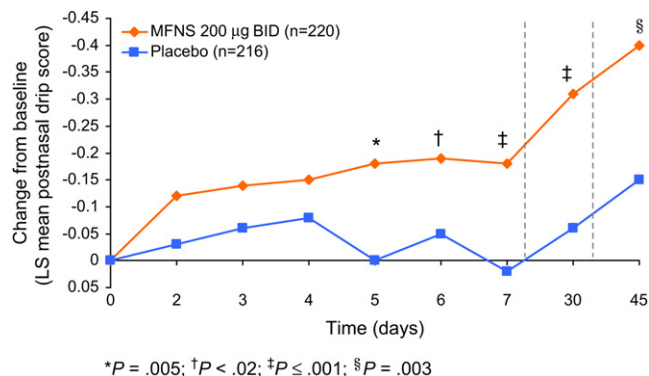
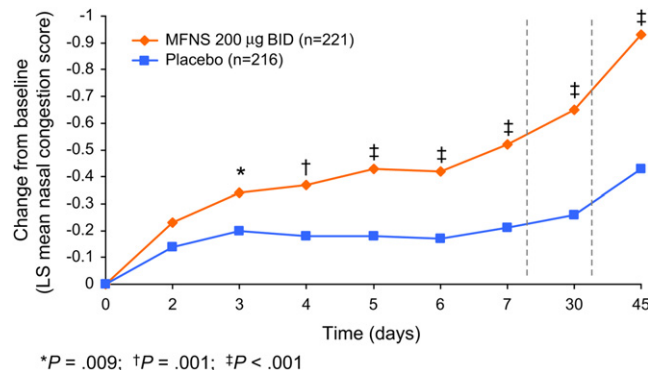
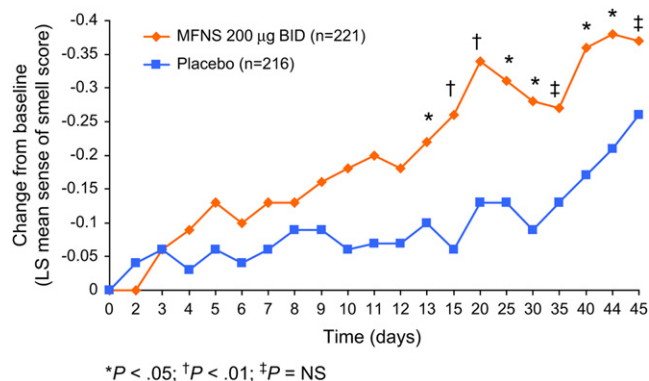
PNIF

A statistically significant increase in PNIF rates in MFNS-treated subjects compared with placebo occurred on day 2, with an increase of 6.22 L/min (9.2%) vs 1.48 L/min (2.1%), a treatment effect of 4.74 L/min (95% CI, 0.43 - 9.05 ; $P = .031$). The difference between MFNS and placebo was not significant on day 3, but returned to significance on day 4, with an increase of 11.98 L/min (18.4%) for MFNS compared with 2.50 L/min (2.1%) for placebo. This treatment effect was 9.38 L/min (95% CI, 4.71 - 14.26 ; $P < .001$), and continued through day 7 (18.19 L/min [30.1%]

TABLE II. Change in symptom scores from baseline at days 7, 14, 30, and 45 by treatment groups

Symptom	MFNS 200 µg twice daily (n = 224)					Placebo (n = 223)				
	Baseline	Day 7	Day 14	Day 30	Day 45	Baseline	Day 7	Day 14	Day 30	Day 45
Anterior rhinorrhea	1.62	1.35 (<i>P</i> < .001)	1.19 (<i>P</i> < .001)	1.08 (<i>P</i> < .001)	1.05 (<i>P</i> < .001)	1.62	1.65	1.51	1.48	1.42
Congestion/obstruction	2.28	1.76 (<i>P</i> < .001)	1.59 (<i>P</i> < .001)	1.44 (<i>P</i> < .001)	1.35 (<i>P</i> < .001)	2.25	2.11	2.00	1.93	1.82
Postnasal drip	1.46	1.28 (<i>P</i> < .001)	1.14 (<i>P</i> = .001)	1.07 (<i>P</i> < .001)	1.06 (<i>P</i> = .003)	1.48	1.50	1.38	1.46	1.33
Loss of sense of smell	2.04	1.91 (<i>P</i> = NS)	1.80 (<i>P</i> = .008)	1.76 (<i>P</i> = .011)	1.67 [†] (<i>P</i> = NS)	2.15	2.09	2.07	2.06	1.89
PNIF (L/min)*	92.20	101.39 (<i>P</i> < .001)	114.94 (<i>P</i> < .001)	124.94 (<i>P</i> < .001)	126.60 (<i>P</i> < .001)	89.20	92.94	96.62	96.91	96.05

*Normal PNIF is 100-300 L/min. Higher score indicates improvement.

[†]*P* < .05 on day 44.**FIG 1.** LS mean change in anterior rhinorrhea score from days 2 to 45 with MFNS 200 µg twice daily (BID) vs placebo.**FIG 3.** LS mean change in postnasal drip score from days 2 to 45 with MFNS 200 µg twice daily (BID) vs placebo.**FIG 2.** LS mean change in nasal congestion score from days 2 to 45 with MFNS 200 µg twice daily (BID) vs placebo.**FIG 4.** LS mean change in sense of smell score from days 2 to 45 with MFNS 200 µg twice daily (BID) vs placebo.

MFNS vs 3.74 L/min [5.6%] placebo), when the treatment effect was 14.45 L/min (95% CI, 9.16-19.74; *P* < .001). The maximum treatment effect was reached on day 41, with a 56.7% increase. MFNS-treated subjects continued to show improvement in PNIF rates every day until day 45 (*P* < .001; Fig 5, Table II).

Bilateral polyp grade

As previously reported,^{17,19} change in bilateral polyp grade reached statistical significance after 1 month of treatment,

the first period assessed, with a decrease from baseline of −0.56 (−11.4%) with MFNS compared with −0.33 (−6.7%) with placebo, a treatment effect of −0.23 (95% CI, −0.41 to −0.04; *P* ≤ .03). The decrease in polyp grade scores with MFNS remained statistically significant for each of the remaining 3 months measured, with a reduction at month 4, when maximum treatment effect was reached, of −1.13 (−28.1%) with MFNS vs −0.82 (−19.4%) with placebo. The treatment effect at month 4 was −0.31 (95% CI, −0.59 to −0.03; *P* = .03; Fig 6).

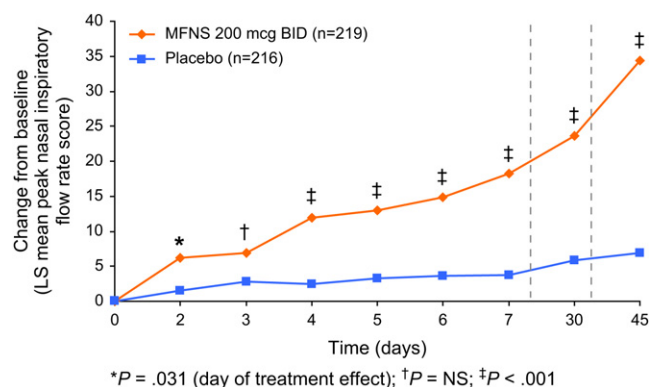


FIG 5. LS mean change in PNIF rate from days 2 to 45 with MFNS 200 μ g twice daily (BID) vs placebo.

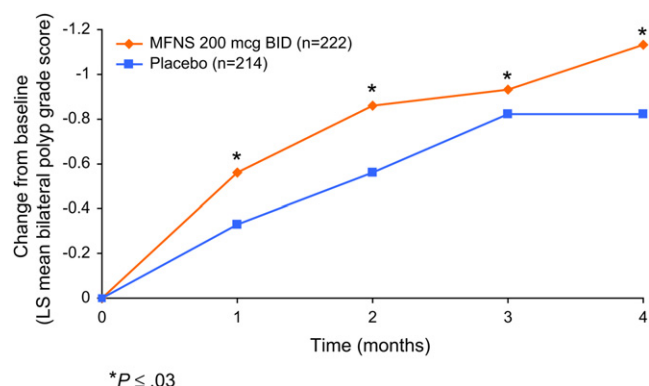


FIG 6. LS mean change in bilateral polyp grade from months 1 to 4 with MFNS 200 μ g twice daily (BID) vs placebo.

DISCUSSION

Mometasone furoate 200 μ g twice daily significantly improves the serious and troublesome symptoms of nasal congestion/obstruction, rhinorrhea, postnasal drip, and loss of sense of smell within 2 (24 hours after the first dose) to 5 days of initiating therapy for most symptoms, and at day 13 for sense of smell. As previously reported, this treatment effect persists for at least 4 months.^{17,19} In this study, MFNS-treated subjects experienced significant improvement in anterior rhinorrhea, nasal congestion/obstruction, and postnasal drip on days 2, 3, and 5, respectively, whereas improvement in sense of smell occurred before the end of the second week of treatment.

Fifty-seven percent of MFNS 200 μ g twice-daily recipients were considered to be improved in our previous study.¹⁷ Improvement in bilateral polyp grade occurred by 1 month of treatment, although this is the first time point evaluated. Because reducing nasal polyp size is a slow process, this degree of improvement is important.^{17,19} Finally, our previous studies revealed that incremental improvements in polyp grade scores continued throughout the 4-month study period, suggesting that treatment with MFNS should be continued to achieve a full response.

For many patients, loss of the sense of smell is one of the most disturbing symptoms of nasal polyposis.¹⁸ As a result, return of sense of smell remains an important therapeutic goal of therapy. In the 2 previous studies,^{17,19} baseline symptom scores indicated that subjects found nasal congestion/obstruction and loss of sense

of smell to be more serious than other nasal symptoms, as has been previously reported.^{16,20} From this data analysis, subjects experienced a statistically significant improvement in sense of smell on day 13, which persisted for the 4-month study period.^{17,19} The lack of statistical significance for improvement of sense of smell on individual days may be secondary to the observed placebo effect. Alternatively, change in sense of smell may be more subjective than other symptoms of nasal polyposis. For example, it has recently been shown that both retronasal and anterior stimulation of the olfactory epithelium is necessary for smell. The retronasal pathway is important in anterior nasal obstruction from polyps, in which odor identification is more effective through a retronasal route.²¹ Surgery has very little effect on hyposmia,²² supporting the importance of medical therapy in treating this serious symptom of nasal polyposis.

The rapid onset of action of MFNS on nasal polyposis is consistent with previous studies of MFNS in allergic rhinitis.^{23,24} In these studies, subjects achieved symptom relief within 12 hours of starting therapy. This rapid onset of action may in part be a result of the high topical potency of MFNS in inhibiting the synthesis and release of proinflammatory mediators such as IL-1, IL-5, IL-6, and TNF. It may also form complexes with transcription factors for proinflammatory molecules.^{23,25}

The effect of MFNS on the symptoms of nasal polyposis increases with the duration of therapy. In this study, improvement in symptom scores was greater at day 7 for anterior rhinorrhea, congestion, postnasal drip, and PNIF than on the first day of statistical significance. Similarly, improvement continued for all symptoms until day 45. The only exception was in sense of smell, for which symptoms improved significantly on all but 6 days after reaching significance on day 13. This improvement in symptom scores corresponds to the increased improvement in polyp grade scores over time.^{17,19}

Nasal polyposis may require a longer duration of therapy than that required for rhinosinusitis because MFNS treatment only gradually reduces polyp grade scores.¹⁷ In addition, the presence of nasal polyps may alter the distribution of intranasal corticosteroids in the nasal cavity.^{2,19} Finally, nasal polyposis is associated with multiple histologic changes, including edema and fibrosis, decreased vascularization, and a reduced number of glands and nerve endings in an often damaged epithelium, which may interfere with therapy.² It is unclear whether these changes are reversed by topical corticosteroid treatment. Further studies are needed to determine the lasting effect of MFNS nasal spray on the continued resolution of nasal symptoms associated with nasal polyposis, because the maximal reduction in polyp size may take several months to achieve.^{13,15,17,26}

A pronounced placebo effect was observed in this analysis, particularly with the end points of nasal congestion/obstruction and sense of smell. This placebo effect increased with time and was apparent for most of the end points in the 2 studies.^{17,19} The placebo effect has been observed in other studies of intranasal corticosteroids in nasal polyposis^{13,27} and may be attributable to the nonactive components of MFNS.¹⁹ In previous allergic rhinitis studies, a pronounced placebo effect was also seen, especially when the placebo was a liquid suspension with beneficial effects on the nasal mucosa.²⁸ Thus, the use of placebo groups in future nasal polyposis trials is important to ensure that a true measure of treatment benefit is attained.¹⁹

Mometasone furoate 200 μ g twice daily significantly improves the troublesome symptoms of nasal congestion/obstruction,

rhinorrhea, and postnasal drip in subjects with nasal polyposis. Significant improvement in all symptoms but sense of smell begins between 2 and 5 days after the first dose. In addition, peak nasal flow, an indication of nasal obstruction, improves by day 2 of therapy. Importantly, significant improvement in sense of smell, the most troublesome symptom of nasal polyposis, occurs before the end of the second week of treatment. Thus, MFNS 200 µg twice daily is an effective medical treatment for nasal polyposis, with rapid onset and lasting relief of most of the major symptoms of nasal polyposis within 2 (24 hours after the first dose) to 5 days of initiating therapy.

Editorial assistance was provided by Adelphi-Eden Health Communications.

Clinical implications: MFNS provides rapid relief from the symptoms of nasal polyposis.

REFERENCES

- Hedman J, Kaprio J, Poussa T, Nieminen MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *Int J Epidemiol* 1999;28:717-22.
- Bachert C, Hormann K, Mosges R, Rasp G, Richelmann H, Muller R, et al. An update on the diagnosis and treatment of sinusitis and nasal polyposis. *Allergy* 2003;58:176-91.
- Delank KW, Stoll W. [Sense of smell before and after endonasal surgery in chronic sinusitis with polyps.] *HNO* 1994;42:619-23.
- Bachert C, van Zele T, Gevaert P, De Schrijver L, Van Cauwenberge P. Superantigens and nasal polyps. *Curr Allergy Asthma Rep* 2003;3:523-31.
- Simon HU, Yousefi S, Schranz C, Schapowal A, Bachert C, Blaser K. Direct demonstration of delayed eosinophil apoptosis as a mechanism causing tissue eosinophilia. *J Immunol* 1997;158:3902-8.
- Bachert C, Wagenmann M, Hauser U, Rudack C. IL-5 synthesis is upregulated in human nasal polyp tissue. *J Allergy Clin Immunol* 1997;99:837-42.
- Bachert C, Gevaert P, Holtappels G, Cuvelier V, van Cauwenberge P. Nasal polyposis: from cytokines to growth. *Am J Rhinol* 2000;14:279-90.
- Deuschl H, Drettner B. Nasal polyps treated by beclomethasone nasal aerosol. *Rhinology* 1977;15:17-23.
- Jankowski R, Schrevelius C, Bonfils P, Sabin Y, Gilain L, Prades J-M, et al. Efficacy and tolerability of budesonide aqueous nasal spray treatment in patients with nasal polyps. *Arch Otolaryngol Head Neck Surg* 2001;127:447-52.
- Tos M, Svendsstrup F, Arndal H, Orntoft S, Jakobsen J, Borum P, et al. Efficacy of an aqueous and a powder formulation of nasal budesonide compared in patients with nasal polyps. *Am J Rhinol* 1998;12:183-9.
- Filiaci F, Passali D, Puxeddu R, Schrewelius C. A randomized controlled trial showing efficacy of once daily intranasal budesonide in nasal polyposis. *Rhinology* 2000;38:185-90.
- Lund VJ, Flood J, Sykes AP, Richards DH. Effect of fluticasone in severe polyposis. *Arch Otolaryngol Head Neck Surg* 1998;124:513-8.
- Ruhno J, Andersson B, Denburg J, Anderson M, Hitch D, Lapp P, et al. A double-blind comparison of intranasal budesonide with placebo for nasal polyposis. *J Allergy Clin Immunol* 1990;86:946-53.
- Lildholdt T, Rundcrantz H, Lindqvist N. Efficacy of topical corticosteroid powder for nasal polyps: a double-blind, placebo-controlled study of budesonide. *Clin Otolaryngol Allied Sci* 1995;20:26-30.
- Vendelbo Johansen L, Illum P, Kristensen S, Winther L, Vang Petersen S, Synnerstad B. The effect of budesonide (Rhinocort®) in the treatment of small and medium-sized nasal polyps. *Clin Otolaryngol Allied Sci* 1993;18:524-7.
- Johansson L, Bramerson A, Holmberg K, Melen I, Akerlund A, Bende M. Clinical relevance of nasal polyps in individuals recruited from a general population-based study. *Acta Otolaryngol* 2004;124:77-81.
- Small CB, Hernandez J, Reyes A, Schenkel E, Damiano A, Stryzak P, et al. Efficacy and safety of mometasone furoate nasal spray in nasal polyposis. *J Allergy Clin Immunol* 2005;116:1275-81.
- Badia L, Lund V. Topical corticosteroids in nasal polyposis. *Drugs* 2001;61:573-8.
- Stjärne P, Mösges R, Jorissen M, Passali D, Bellussi L, Staudinger H, et al. A randomized controlled trial of mometasone furoate nasal spray for the treatment of nasal polyposis. *Arch Otolaryngol Head Neck Surg* 2006;132:179-85.
- Rowe-Jones JM, Mackay IS. Management of nasal polyps. *Curr Opin Otolaryngol Head Neck Surg* 1998;6:41-6.
- Holbrook EH, Leopold DA. An updated review of clinical olfaction. *Curr Opin Otolaryngol Head Neck Surg* 2006;14:23-8.
- Blomqvist EH, Lundblad L, Anggard A, Haraldsson PO, Stjärne P. A randomized controlled study evaluating medical treatment versus surgical treatment in addition to medical treatment of nasal polyposis. *J Allergy Clin Immunol* 2001;107:224-8.
- Bronsky EA, Aaronson DW, Berkowitz RB, Chervinsky P, Graft D, Kaiser HB, et al. Dose ranging study of mometasone furoate (Nasonex) in seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 1997;79:51-6.
- Berkowitz RB, Bernstein DI, LaForce C, Pedinoff AJ, Rooklin AR, Damaraju CRV, et al. Onset of action of mometasone furoate nasal spray (NASONEX®) in seasonal allergic rhinitis. *Allergy* 1999;54:64-9.
- Adcock IM, Stevens DA, Barnes PJ. Interactions of glucocorticoids and β₂-agonists. *Eur Respir J* 1996;9:160-8.
- Holmberg K, Juliusson S, Balder B, Smith DL, Richards DH, Karlsson G. Fluticasone propionate aqueous nasal spray in the treatment of nasal polyposis. *Ann Allergy Asthma Immunol* 1997;78:270-6.
- Mygind N, Pedersen CB, Prytz S, Sorensen H. Treatment of nasal polyps with intranasal beclomethasone dipropionate aerosol. *Clin Allergy* 1975;5:159-64.
- Berkowitz RB, Roberson S, Zora J, Capano D, Chen R, Lutz C, et al. Mometasone furoate nasal spray is rapidly effective in the treatment of seasonal allergic rhinitis in an outdoor (park), acute exposure setting. *Allergy Asthma Proc* 1999;20:167-72.