

Safety and efficacy of mometasone furoate aqueous nasal spray in children with allergic rhinitis: Results of recent clinical trials

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Intranasal mometasone furoate (MF) has been extensively studied in adults and has been found to be safe and effective therapy for the treatment of allergic rhinitis. Several studies have now been conducted on pediatric patients. In all, 990 pediatric patients given mometasone furoate nasal spray (MFNS) have been studied in phase I, II, and III clinical trials. In a dose-ranging study, 5 doses of nasal spray (25, 100, and 200 µg MFNS daily and 168 µg beclomethasone dipropionate daily) were compared with placebo. The 100- and 200-µg daily doses of MFNS were found to be more effective than 168 µg beclomethasone dipropionate or 25 µg MFNS given daily. MFNS (100 µg once daily) was chosen as the appropriate dose. In clinical efficacy and safety trials, MFNS was given to 381 patients 3 to 11 years of age for 4 weeks (357 patients received 100 µg MFNS daily for 6 months) and was found to decrease symptom scores from baseline significantly better than placebo. The long-term safety of MFNS was also studied in 166 patients treated for one year; no significant changes in intraocular pressure were detected. Cosyntropin stimulation showed no decreases in cortisol. In adults, nasal mucosa showed improvement in appearance of epithelium and reduction of inflammatory infiltrates, and there were no signs of nasal atrophy. (J Allergy Clin Immunol 2001;108:S54-8.)

Key words: Beclomethasone dipropionate, cosyntropin, hypothalamic pituitary axis, mometasone furoate

The goal of pharmacotherapy in children with allergic rhinitis (AR) is to alleviate the associated symptoms by prescribing effective medications with the lowest potential for side effects. These should be administered as infrequently as possible. Nasal topical steroids have been proven to be safe and effective in the treatment and prophylaxis of seasonal AR and in the treatment of perennial rhinitis in adults,¹⁻¹¹ controlling the signs and symptoms of both the immediate and late phases of the allergic response to allergens.²

Mometasone furoate nasal spray (MFNS), an intranasal corticosteroid, is a highly potent, synthetic 17-heterocyclic glucocorticoid commercially available as an

Abbreviations used

AR: Allergic rhinitis
BDP: Beclomethasone dipropionate
HPA: Hypothalamic-pituitary-adrenal
MF: Mometasone furoate
MFNS: Mometasone furoate nasal spray

aqueous suspension nasal spray. It is virtually undetectable in plasma after intranasal and oral administration and has an absolute bioavailability of <0.1% in healthy volunteers.⁴ When MFNS was administered at up to 20 times the clinically selected adult dose of 200 µg once daily, it was not associated with suppression of the hypothalamic-pituitary-adrenal (HPA) axis.⁴

MOMETASONE FUROATE STUDIES IN ADULTS

The safety and efficacy of MFNS in the prophylaxis and treatment of seasonal AR and the treatment of perennial AR in adults has been extensively studied.⁴⁻¹⁰ Hebert et al⁶ showed that 100 or 200 µg MFNS once daily was effective in relieving moderate to severe symptoms of seasonal AR. Graft et al⁷ demonstrated that once-daily MFNS, administered approximately 4 weeks before the onset of the ragweed season, was effective and well tolerated in the prophylactic treatment of seasonal AR in adults. Drouin et al⁸ concluded that 200 µg MFNS once daily was significantly more effective than placebo in relieving symptoms of perennial AR in patients 12 years of age and older, establishing it as an effective and well-tolerated alternative to intranasal steroids requiring twice-daily administration for treatment of moderate to severe symptoms of perennial AR.

On the basis of the positive efficacy and safety profile of 200 µg MFNS once daily in the prophylaxis and treatment of seasonal AR and the treatment of perennial rhinitis in adults,⁵⁻¹¹ studies were initiated to determine the safest and lowest possible effective dose of MFNS in the treatment of seasonal and perennial AR in children.

MOMETASONE FUROATE STUDIES IN CHILDREN

The pediatric studies that were initiated consisted of 3 phase I studies involving 94 patients, 1 phase II study, and 3 phase III studies (enrolling a total of 990 subjects).

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Safety studies were conducted before and after 12 months of treatment with mometasone furoate aqueous nasal spray to assess the potential for glaucoma and/or posterior cataracts.¹² To examine the effects of mometasone furoate on growth, a knemometry study¹³ was performed to assess short-term lower-leg growth and a 1-year growth study was conducted to assess the effects of MFNS on statural growth.¹⁴

In a study conducted by Brannan et al¹⁵ in children 6 to 12 years of age, the plasma levels of mometasone furoate were too low to be quantified (<50 pg/mL) after 14 days of MFNS treatment of up to 200 µg daily; the children showed no detectable HPA axis suppression.

DOSE-RANGING STUDY OF MOMETASONE FUROATE AQUEOUS NASAL SPRAY IN CHILDREN WITH SEASONAL ALLERGIC RHINITIS

Meltzer et al¹⁶ conducted a dose-ranging and systemic safety profile of mometasone furoate aqueous nasal spray in children 6 to 11 years old with seasonal AR in a 4-week, multicenter, randomized, double-blind, active and placebo-controlled, parallel-group study. The patients were randomly assigned to 1 of 5 treatment arms: 137 patients were treated with 25 µg MFNS daily, 135 with 100 µg MFNS daily, 133 with 200 µg MFNS daily, 138 with 84 µg beclomethasone dipropionate (BDP) twice daily, and 136 patients with placebo (Fig 1). The physician-rated total nasal symptom scores were analyzed on days 4, 8, 15, and 29. All doses of MFNS and BDP were significantly more effective in reducing total nasal symptom scores than was placebo ($P < .02$) during the first week of treatment. As treatment continued with 100 µg MFNS daily, 200 µg MFNS daily, or 84 µg BDP twice daily, the mean of nasal symptom scores decreased further from baseline evaluation. MFNS (25 µg daily) was significantly less effective than were the other active treatments and did not show a statistically significant effect compared with placebo at day 29 or end point evaluation. The dose of 200 µg MFNS daily offered no additional effectiveness compared with 100 µg MFNS daily. Figure 2 illustrates the change in physician-rated symptom scores for each of the treatment groups.

The patient-rated total nasal symptom scores for days 1 to 15 show that 100 µg MFNS daily, 200 µg MFNS daily, and 84 µg BDP daily were more effective than 25 µg MFNS daily and superior to the placebo group ($P < .01$). On days 16 to 29, 100 and 200 µg MFNS daily and 84 µg BDP twice daily were significantly more effective than 25 µg MFNS daily and placebo. Figure 3 illustrates the change in patient-rated symptom scores for each of the treatment groups.

Mean plasma cortisol values at baseline and after 4 weeks of treatment in all patients assessed showed a normal response to cosyntropin stimulation testing among the 5 treatment groups, as illustrated in Figure 4. Based on the results of this study, 100 µg MFNS daily was selected as the most appropriate dose of MFNS for children from 3 to 11 years of age with seasonal or perennial AR.

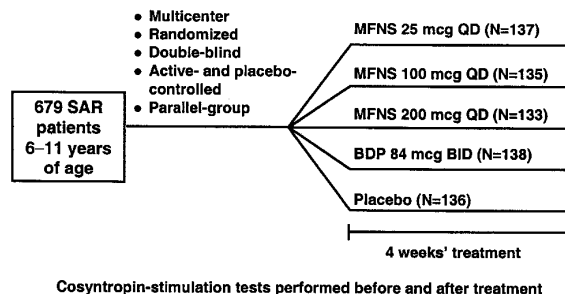


FIG 1. Dose-ranging study of mometasone furoate nasal spray once daily in children with seasonal allergic rhinitis (From Meltzer EO, Berger WE, Berkowitz RB, Bronsky EA, Dvorin DJ, Finn AF, et al. A dose-ranging study of mometasone furoate aqueous nasal spray in children with seasonal allergic rhinitis. *J Allergy Clin Immunol* 1999;104:107-14. With permission).

EFFICACY AND SAFETY OF MOMETASONE FUROATE AQUEOUS NASAL SPRAY IN CHILDREN WITH PERENNIAL RHINITIS

In a phase III study¹⁷ designed to assess the efficacy and safety of MFNS in children with perennial AR, 381 patients between 3 and 11 years of age were included. To evaluate efficacy, the patients were randomly assigned in a double-blind, placebo-controlled study. During 4 weeks, 190 patients received 100 µg MFNS daily and 191 patients received placebo. To evaluate safety, the study continued as an open-label study, with 357 patients receiving 100 µg MFNS daily for 6 months.

The physician-rated total nasal symptom scores showed a mean decrease of symptoms compared with baseline, which was significantly greater than the decrease with placebo ($P < .02$) from day 8 to end point evaluation. Figure 4 illustrates the change in physician-rated symptom scores for both treatment groups. The patient-rated total nasal symptom score, shown in Figure 5, showed a significant mean decrease from baseline over placebo on days 1 to 15, days 16 to 29, and during end point evaluation ($P < .01$).

In this study, treatment-related adverse events were epistaxis, sneezing, coughing, and headache, which were reported as mild in most cases. There were no changes in laboratory test results, vital signs, electrocardiograms, physical examinations, or nasal examinations during the study.

In a phase III study¹² performed to assess long-term safety of 100 µg MFNS daily, 251 patients 6 to 11 years of age were enrolled in an active-controlled, evaluator-blinded, randomized, multicenter study lasting 1 year. The patients were randomly assigned to 2 groups: 166 patients received 100 µg MFNS daily and 85 patients received 168 µg BDP daily for 12 months. A complete ophthalmologic evaluation that included tonometry and slit-lamp examinations for detection of glaucoma and cataracts was performed before and after 12 months of treatment. No significant changes from baseline intraocular pressure or posterior subcapsular cataracts were detected at end point evaluation for either treatment group.

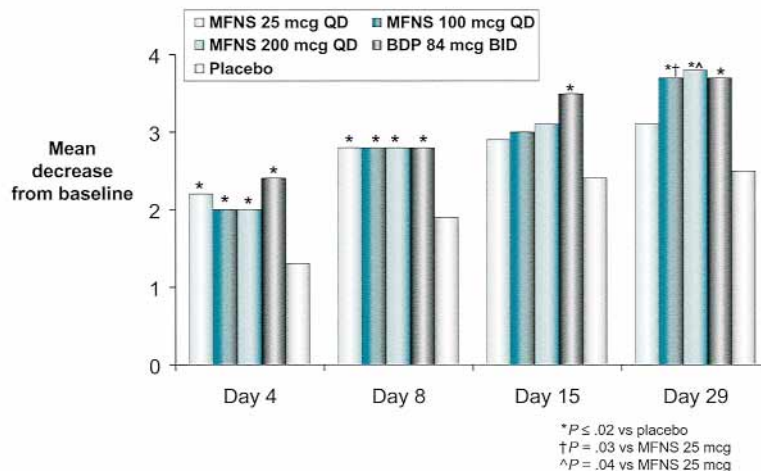


FIG 2. Physician-rated total nasal symptom scores (From Meltzer EO, Berger WE, Berkowitz RB, Bronsky EA, Dvorin DJ, Finn AF, et al. A dose-ranging study of mometasone furoate aqueous nasal spray in children with seasonal allergic rhinitis. *J Allergy Clin Immunol* 1999;104:107-114. With permission).

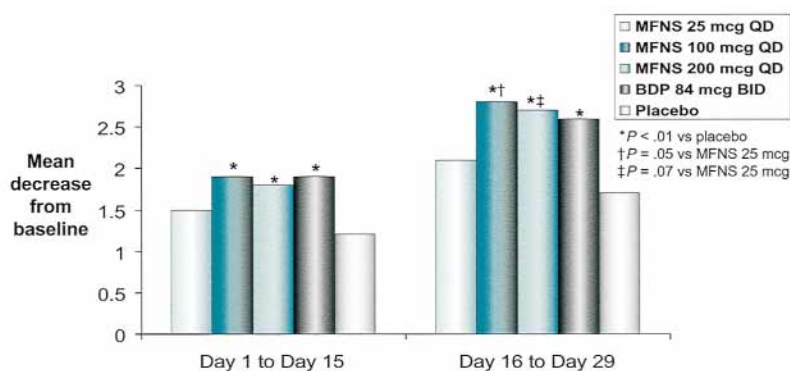


FIG 3. Patient-rated total nasal symptom scores (From Meltzer EO, Berger WE, Berkowitz RB, Bronsky EA, Dvorin DJ, Finn AF, et al. A dose-ranging study of mometasone furoate aqueous nasal spray in children with seasonal allergic rhinitis. *J Allergy Clin Immunol* 1999;104:107-114. With permission).

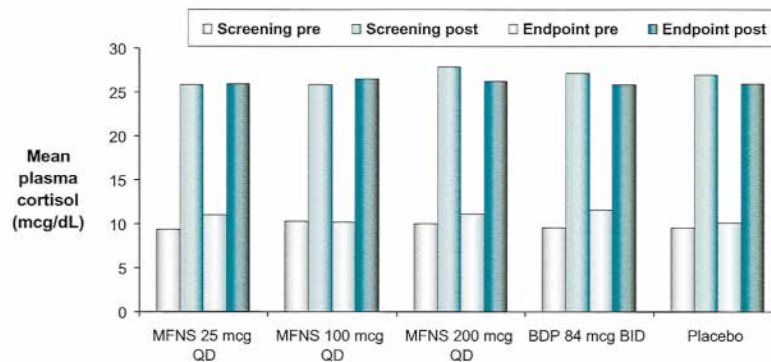


FIG 4. Mean plasma cortisol values before and after cosyntropin stimulation (From Meltzer EO, Berger WE, Berkowitz RB, Bronsky EA, Dvorin DJ, Finn AF, et al. A dose-ranging study of mometasone furoate aqueous nasal spray in children with seasonal allergic rhinitis. *J Allergy Clin Immunol* 1999;104:107-114. With permission).

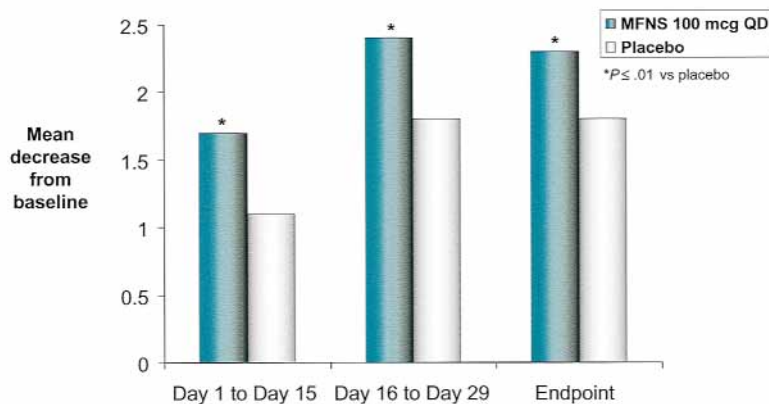


FIG 5. Patient-rated total nasal symptom scores (unpublished data; Schering-Plough Research Institute; study report I96-090).

Cosyntropin stimulation testing was performed at weeks 26 and 52 in 69 patients. The mean plasma cortisol levels, before and after cosyntropin stimulation testing, showed no clinically relevant decreases in the mean basal or in the stimulated plasma cortisol measurements from screening to weeks 26 and 52 in both treatment groups, nor was there evidence of clinical suppression of the HPA axis in either group. Plasma concentrations of mometasone furoate were all below the limit of quantification (<50 pg/mL) in the patients tested.

In this study, treatment-related adverse events occurred in >2% of patients. The incidence of adverse events was similar in both active medications. Epistaxis, headache, and pharyngitis were the most frequent adverse events but were reported as mild in most cases. There were no changes in laboratory test results, electrocardiograms, vital signs, physical examinations, or nasal examinations during the study.

Because the HPA axis response is one of the most sensitive tests for systemic exposure to steroids, the effects of MFNS on plasma cortisol were evaluated before and after cosyntropin-stimulation testing. In studies in a pediatric population, MFNS had no significant effect on the HPA axis, even when administered up to 20 times the recommended dose or up to 1-year duration in children 3 to 11 years of age.^{12,16} No significant changes from baseline intraocular pressure or posterior subcapsular cataracts were detected after 12 months of treatment for either treatment group.¹²

A randomized, placebo-controlled, double-blind, multicenter study was conducted on 98 patients between the ages of 3 and 9 years of age with perennial rhinitis to determine whether treatment with MFNS results in suppression of growth. Patients were randomly assigned to treatment with either 100 µg MFNS daily or placebo. After 1 year of treatment, there was no suppression of growth in the MFNS group; the authors concluded that 1-year treatment with MFNS was well tolerated and resulted in no evidence of retardation of growth or suppression of the HPA axis function in patients with perennial rhinitis.¹⁴

The use of intranasal corticosteroids may increase the risk of mucosal irritation, dryness, crusting, bleeding, and septal perforations. All patients who use a nasal topical steroid must be cautioned to consult their physician in cases of persistent nasal irritation, crusting, or epistaxis. However, biopsies of the nasal mucosa before and after 1-year treatment with MFNS in adults showed improvement of the appearance of the epithelium and reduction of the inflammatory cell infiltrate, particularly eosinophils and mast cells, and no signs of nasal mucosa atrophy.¹⁸

Overall, the incidence of adverse events in children treated with MFNS was comparable to that in patients given placebo or the active control. The most frequent treatment-related adverse events in children were epistaxis, pharyngitis, sneezing, and headache. Most adverse events were described as mild and of short duration. No subcapsular cataracts were detected, nor changes from mean intraocular pressures for either treatment group. No clinically relevant changes in vital signs, electrocardiograms, clinical laboratory values, or nasal examinations were reported for the MFNS-treated group.

CONCLUSIONS

MFNS (100 µg daily) is the optimal dosage that can provide significant efficacy and a favorable safety profile for children 3 to 11 years of age with seasonal and perennial AR. In children 3 to 11 years of age with seasonal AR, 100 µg MFNS daily provides greater symptomatic relief than a placebo and relief similar to 84 µg BDP twice daily. In addition, MFNS has a low potential for systemic effects because plasma concentrations of mometasone furoate in children were virtually undetectable in the 119 postdose samples tested (<50 pg/mL). There was no evidence of HPA axis suppression in the patients tested with cosyntropin stimulation before and after treatment.

In addition, MFNS was well tolerated in studies of pediatric AR. The efficacy and safety of 100 µg MFNS daily indicate that this agent is a useful addition to the clinician's armamentarium for the treatment of pediatric AR.

REFERENCES

1. Lund V. International Consensus Report on the Diagnosis and Management of Rhinitis: International Rhinitis Management Working Group. *Allergy* 1994;49:1-34.
2. Meltzer EO. Treatment options for the child with allergic rhinitis. *Clin Pediatr (Phila)* 1998;37:1-10.
3. Tarlo SM, Cockcroft DW, Dolovich J, Hargreave FE. Beclomethasone dipropionate aerosol in perennial rhinitis. *J Allergy Clin Immunol* 1977;59:232-6.
4. Brannan M, Seiberling M, Cutler D, Cuss F, Affrime M. Lack of systemic activity with intranasal mometasone furoate. *J Allergy Clin Immunol* 1996;97:198.
5. 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.
6. Hebert JR, Nolop K, Lutsky BN. Once-daily mometasone furoate aqueous nasal spray (Nasonex) in seasonal allergic rhinitis: an active- and placebo-controlled study. *Allergy* 1996;51:569-76.
7. Graft D, Aaronson D, Chervinsky P, Kaiser H, Melamed J, Pedinoff A, 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.
8. Drouin M, Yang WH, Bertrand B, Van Cauwenberge P, Clement P, Dalby K, et al. Once daily mometasone furoate aqueous nasal spray is as effective as twice daily beclomethasone dipropionate for treating perennial allergic rhinitis patients. *Ann Allergy Asthma Immunol* 1996;77:153-60.
9. 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; discussion 22-23.
10. Mandl M, Nolop K, Lutsky BN. Comparison of once daily mometasone furoate (Nasonex) and fluticasone propionate aqueous nasal sprays for the treatment of perennial rhinitis: 194-079 Study Group. *Ann Allergy Asthma Immunol* 1997;79:370-8.
11. Onrust SV, Lamb HM. Mometasone furoate: a review of its intranasal use in allergic rhinitis. *Drugs* 1998;56:725-45.
12. Clin Doc 98251799. One year, evaluator-blind safety study of mometasone furoate (SCH 32088) nasal spray versus beclomethasone dipropionate in children (ages 6 to 11) with perennial rhinitis (study report for protocol 196-091). Kenilworth, NJ: Schering-Plough Research Institute; 1998.
13. Agertoft L, Wolthers OD, Fuglsang G, Pedersen S. Nasal powder administration of budesonide for seasonal rhinitis in children and adolescents. *Pediatr Allergy Immunol* 1993;4:152-6.
14. Schenkel E, Skoner D, Bronsky E, Miller D, Pearlman D, Rooklin A, et al. Absence of growth retardation in children with perennial allergic rhinitis following 1 year of treatment with mometasone furoate aqueous nasal spray. *Pediatrics* 2000;105:e22.
15. 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.
16. Meltzer EO, Berger WE, Berkowitz RB, Bronsky EA, Dvorin DJ, Finn AF, et al. A dose-ranging study of mometasone furoate aqueous nasal spray in children with seasonal allergic rhinitis. *J Allergy Clin Immunol* 1999;104:107-14.
17. Clin Doc 9827653. Four-week, double-blind efficacy and safety of mometasone furoate (SCH 32088) aqueous nasal spray vs placebo, followed by six-month, open-label safety in children with perennial rhinitis (study report for protocol 196-090). Kenilworth, NJ: Schering Plough Research Institute; 1998.
18. Minshall E, Ghaffar O, Cameron L, O'Brien F, Quinn H, Rowe-Jones J, et al. Assessment by nasal biopsy of long-term use of mometasone furoate aqueous nasal spray (Nasonex) in the treatment of perennial rhinitis. *Otolaryngol Head Neck Surg* 1998;118:648-54.