

Safety of mometasone furoate nasal spray in the treatment of nasal polyps in children

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Abstract

Background: Mometasone furoate nasal spray (MFNS) improves nasal symptoms and reduces polyp size in adults with nasal polyposis. This 4-month, multinational, randomized, double-blind study was conducted to assess the safety of MFNS in pediatric subjects aged 6–17 yr.

Methods: Subjects aged 6–11 yr with bilateral nasal polyps received MFNS 100 µg once or twice daily or placebo; those aged 12–17 yr received MFNS 200 µg once or twice daily or placebo. End-points included change in 24-h urinary free cortisol (primary), change in 24-h urinary free cortisol corrected for creatinine (key secondary), and adverse events. Efficacy parameters included polyp size, nasal symptoms, and investigator-evaluated therapeutic response, although the study was not powered for statistical analysis of efficacy.

Results: Least squares baseline mean urinary free cortisol level (nmol/24 h) for both age groups combined (N = 127) was 49.5 in the MFNS once-daily group, 39.6 in the MFNS twice-daily group, and 49.8 in the placebo group. Change in 24-h urinary free cortisol did not significantly differ among MFNS- and placebo-treated subjects. Least squares mean 24-h urinary free cortisol levels corrected for creatinine also showed no significant differences among MFNS- and placebo-treated subjects. No safety issues emerged.

Conclusions: Results of this study confirm the safety profile of MFNS in pediatric patients with bilateral nasal polyps over 4 months, even at double the recommended pediatric dosage for allergic rhinitis.

Nasal polyposis, an inflammatory disorder involving the mucosa of the nose and paranasal sinuses, affects approximately 2–4% of the general population and can have a deleterious effect on quality of life (1, 2). Symptoms include nasal congestion, rhinorrhea, and loss of sense of smell (3). Associations with asthma and allergy have been noted, although the link with nasal polyps to atopy is considered controversial (4). Nasal polyposis occurs rarely in children; one study places the incidence at 0.1% (5) except in children with cystic fibrosis, in whom the incidence may range from 6.7 to 39% (6, 7). A population-based study of over 200,000 Danish citizens found no cases in children under 10 yr of age (8), and a study in the United States that analyzed the medical records of 1051 children from under 1–14 yr of age with asthma or rhinitis at a pediatric clinic identified only one 10-yr-old patient with nasal polyps (6). In a second group of 491 pediatric patients aged 10–19 yr treated at an adult allergy clinic in the

same hospital, only 1.8% had nasal polyps (5). Although nasal polyposis remains uncommon in children, when it occurs, it requires effective therapy.

In the United States, mometasone furoate nasal spray (MFNS) is approved for the treatment of nasal polyposis in individuals aged ≥ 18 yr at a dosage of 200 µg once or twice daily. MFNS is approved for the treatment of allergic rhinitis symptoms in children aged 2–11 yr at a dosage of 100 µg once daily and individuals aged ≥ 12 yr at a dosage of 200 µg once daily. It is also approved for the prophylaxis of seasonal allergic rhinitis in persons aged ≥ 12 yr at a dosage of 200 µg once daily (9). Several studies have demonstrated the safety and efficacy of intranasal corticosteroids, including MFNS, in pediatric populations at dosages used to treat allergic rhinitis (10–13). Few data have been published, however, on the safety of intranasal corticosteroid use in children at the higher dosages necessary to treat nasal polyposis (11, 12, 14, 15). This

study was conducted to evaluate the safety of MFNS in children at dosages appropriate for nasal polyposis (100 µg twice daily for patients aged 6–11 yr and 200 µg twice daily for patients aged 12–17 yr).

Methods

The objective of this study was to determine the safety of MFNS in the treatment of children aged 6–17 yr with nasal polyposis. Children under six were excluded from the study. Efficacy measurements were considered secondary end-points, and only summary data without statistical analysis were calculated.

The study sample was drawn from centers in Europe, Latin America, South Africa, and the United States. All subjects were required to have a diagnosis of bilateral nasal polyposis. Nasal polyps were evaluated endoscopically at the baseline visit. Subjects had a nasal congestion/obstruction score ≥ 1 on a scale of 0 (none) to 3 (severe), rated in the morning according to prior (reflective over the previous 12 h) symptom assessment on each of the last 2 days prior to and on the morning of the baseline visit. Disqualifying criteria (assessed by medical history/physical examination) included antrochoanal polyps, cystic fibrosis, acute rhinosinusitis, rhinitis medicamentosa, dyskinetic ciliary syndromes, and aspirin allergy. Subjects with asthma who received inhaled corticosteroids were required to be on no more than a moderate dosage regimen as defined by 2005 Global Initiative for Asthma Guidelines for ≥ 1 month before screening and to remain on it throughout the study (16); other forms of corticosteroids were prohibited.

Subjects were randomly assigned to one of four treatment groups in a 4:4:1:1 ratio (MFNS once daily:MFNS twice daily: placebo once daily:placebo twice daily) stratified according to age. Those aged 6–11 yr received MFNS 100 µg once daily, MFNS 100 µg twice daily, placebo once daily, or placebo twice daily; those aged 12–17 yr received MFNS 200 µg once daily, MFNS 200 µg twice daily, placebo once daily, or placebo twice daily. Subjects were treated for 4 months and evaluated at day 8 and months 1, 2, 3, and 4. Evaluations included laboratory tests (hematology, blood chemistry, urinalysis), vital signs, and physical examination.

The primary end-point of this safety study was the change in 24-h urinary free cortisol, a measure of hypothalamic–pituitary–adrenal (HPA) axis function, at baseline and study end. A secondary safety end-point was 24-h urinary free cortisol corrected for creatinine. Efficacy end-points included subject-rated signs/symptoms, investigator-evaluated polyp size, and investigator assessment of overall therapeutic response. Signs/symptoms, including nasal congestion/obstruction, anterior rhinorrhea/postnasal drip, and loss of sense of smell, were each rated daily by subjects (with the assistance of a parent or guardian, if needed) on a 4-point scale. Polyp size was assessed at baseline and months 1, 2, 3 and 4, also using a 4-point scale; overall therapeutic response was graded at months 1, 2, 3 and 4 on a 5-point scale ranging from 0 (complete relief) to 4 (no relief). No statistical analysis of efficacy end-points was specified in the study protocol, and only descriptive efficacy statistics were collected.

The study investigators planned to evaluate the primary end-point, change in 24-h urinary free cortisol level, using an analysis of variance (ANOVA) model with treatment and age group as factors. A sample size of 120 subjects (48 in each MFNS group and 24 in the placebo group) was chosen to detect with 80% power a clinically meaningful difference of 32 nm in change from baseline in urinary free cortisol level, assuming a two-tailed alpha of 5%. Because widely disparate baseline values for 24-h urinary free cortisol were noted in different subject groups during the initial analysis of the primary safety end-point, the planned ANOVA was revised in favor of an analysis of covariance (ANCOVA) model that accounted for the effects of age group, treatment, and baseline cortisol values on change in cortisol levels.

Results

The study included 127 subjects: 46 aged 6–11 yr and 81 aged 12–17 yr. Demographics were similar among the treatment groups (Table 1). The study population included 38 subjects in Colombia, 12 in Guatemala, 17 in Honduras, 2 in Panama, 8 in Peru, 14 in Russia, 4 in South Africa, 27 in Ukraine, and 5 in the United States. Of 23 asthmatic subjects, only two were regularly using an inhaled corticosteroid.

Baseline symptom scores were comparable between the groups. The primary analyses were conducted upon all randomized subjects with baseline and any post-baseline 24-h urinary free cortisol levels (MFNS once daily, $n = 44$; MFNS twice daily, $n = 50$; and placebo, $n = 25$). Mean baseline polyp scores were comparable across treatment groups.

Effects on hypothalamic–pituitary–adrenal (HPA) axis function

In the study population, no significant difference in change from baseline in 24-h urinary free cortisol levels was seen between placebo-treated subjects and those treated with MFNS 100/200 µg once ($p = 0.710$ vs. placebo) or twice ($p = 0.453$ vs. placebo) daily (Fig. 1). Change from baseline in urinary free cortisol levels was also not significantly different in subjects aged 6–11 yr receiving placebo or MFNS 100 µg once ($p = 0.253$) or twice ($p = 0.895$) daily (Fig. 1) or in the subgroup aged 12–17 yr receiving placebo and MFNS 200 µg once ($p = 0.237$) or twice ($p = 0.574$) daily (Fig. 1).

Change in 24-h urinary free cortisol was also evaluated by an ANOVA model that included country effect and country-by-treatment interaction. Results indicated no evidence of a significant difference of effect among countries ($p = 0.846$).

The change in 24-h urinary free cortisol corrected for creatinine was not significantly different between MFNS-treated and placebo-treated groups (Table 2).

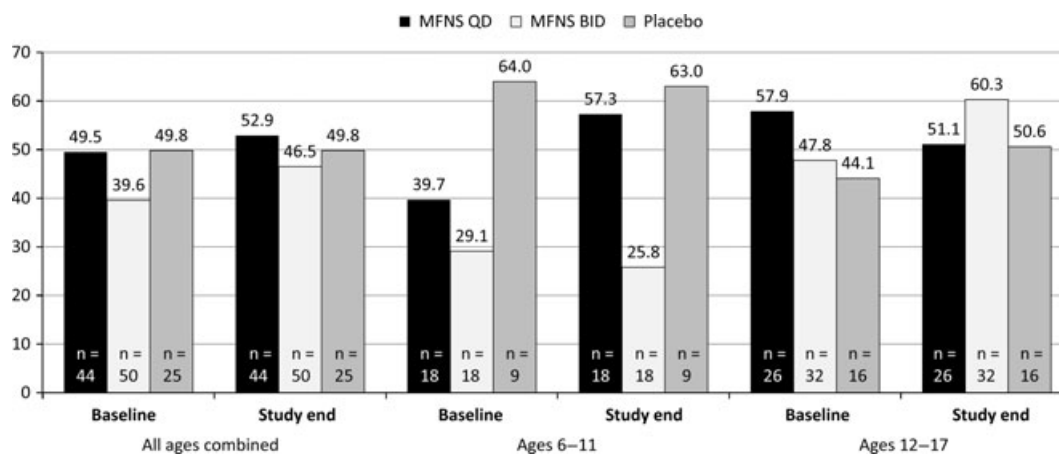
Adverse events

Headache (9%) and epistaxis (8%) were the most frequently reported adverse events (Table 3). Epistaxis was more common in the MFNS arms compared with the pooled placebo arms (6–12% vs. 4%) and was experienced by more subjects in the

Table 1 Demographics of the study population

	MFNS (n = 101)				Pooled Placebo (n = 26)	Total (n = 127)
	6–11 yr		12–17 yr			
	100 µg QD (n = 18)	100 µg BID (n = 18)	200 µg QD (n = 32)	200 µg BID (n = 33)		
Age (yr)						
Mean (s.d.)	9.7 (1.7)	9.6 (1.4)	14.4 (1.8)	14.4 (1.6)	12.7 (3.2)	12.7 (2.9)
Sex, n (%)						
Male	8 (44)	5 (28)	14 (44)	15 (45)	12 (46)	54 (43)
Female	10 (56)	13 (72)	18 (56)	18 (55)	14 (54)	73 (57)
Race, n (%)						
Multiracial	12 (67)	8 (44)	12 (38)	17 (52)	13 (50)	62 (49)
Caucasian	5 (28)	7 (39)	19 (59)	16 (48)	12 (46)	59 (46)
Asian	1 (6)	2 (11)	1 (3)	0	0	4 (3)
Black	0	1 (6)	0	0	1 (4)	2 (2)
Ethnicity, n (%)						
Hispanic	14 (78)	11 (61)	17 (53)	19 (58)	18 (69)	79 (62)
Non-Hispanic	4 (22)	7 (39)	15 (47)	14 (42)	8 (31)	48 (38)
Weight (kg)						
Mean (s.d.)	35.68 (10.10)	35.56 (12.28)	53.19 (12.33)	54.24 (13.16)	43.05 (15.08)	46.41 (14.97)
Asthmatic, n (%)						
Yes	3 (17)	1 (6)	9 (28)	4 (12)	6 (23)	23 (18)
No	15 (83)	17 (94)	23 (72)	29 (88)	20 (77)	104 (82)
Eosinophilic, n (%)*						
Yes	5 (28)	3 (17)	9 (28)	3 (9)	9 (35)	29 (23)
No	13 (72)	15 (83)	23 (72)	30 (91)	17 (65)	98 (77)

MFNS, mometasone furoate nasal spray; s.d., standard deviation.

*Blood eosinophils $\geq 0.45 \times 10^9/\text{l}$.**Figure 1** Urinary free cortisol (nmol/24 h) at baseline and study end for overall population and subgroups by age. LS, least squares; Mometasone furoate nasal spray (MFNS), mometasone furoate nasal spray; UFC, urinary free cortisol. LS for both baseline and study end were based on ANCOVA with treatment, age group, and baseline effects. Study end = last non-missing reading for patient.

MFNS BID groups vs. the MFNS QD groups (11–12% vs. 6%). No clinically meaningful changes in laboratory parameters, vital signs, or physical examinations were seen in any treatment group.

Efficacy findings

The study was not powered to evaluate efficacy. No statistical analysis of efficacy data was specified in the study protocol,

Table 2 Urinary free cortisol corrected for creatinine (nmol/24 h), age groups combined

	MFNS QD (n = 44)	MFNS BID (n = 50)	Placebo (n = 25)
LS mean baseline value	6.7	5.3	7.6
LS mean change, baseline to end-point	0.5*	0.2†	0.6

BID, twice daily; LS, least squares; MFNS, mometasone furoate nasal spray; QD, once daily.

*p = 0.878 vs. placebo.

†p = 0.606 vs. placebo.

Data in this analysis are from all randomized subjects with baseline and any post-baseline 24-h urinary free cortisol levels (n = 119).

Based on ANCOVA with treatment, age group, and baseline effects.

and descriptive statistics only are presented. Sign and symptom scores are shown in Table 4. MFNS given twice daily was associated with the greatest response in polyp size, congestion, and anterior rhinorrhea/postnasal drip. Groups that received MFNS once and twice daily showed numerically greater improvement in congestion compared with placebo. Subjects who received MFNS twice daily had better investigator-assessed therapeutic response compared with those who received placebo.

Discussion

In this 4-month, multicenter, placebo-controlled, randomized study in pediatric polyp patients, MFNS was associated with no significant HPA axis suppression compared with placebo (the primary end-point), even at doses up to 2-fold higher than the pediatric dose recommended to treat allergic rhinitis. Safety of MFNS in this population was further substantiated by the lack of between-group differences in 24-h urinary free cortisol corrected for creatinine, the low incidence and severity of adverse events, and the lack of clinically meaningful changes in laboratory parameters, vital signs, or physical examinations in

the treatment groups. As reported in a long-term trial of MFNS in pediatric subjects with perennial allergic rhinitis including a larger population than was studied here (N = 381), headache and epistaxis were among the most frequently experienced adverse events (13). Though itch/pain/discomfort has been cited as a prominent complaint of children receiving intranasal corticosteroids (17), incidence of such events was low in this study.

These results provide additional information about the safety of MFNS in the pediatric population with nasal polyps and also address lingering concerns regarding the use of intranasal corticosteroids in children. Though intranasal corticosteroids have been occasionally evaluated in children for the treatment of conditions such as adenoidal hypertrophy and otitis media with effusion (18, 19), they are commonly used for allergic rhinitis (20), for which they have US FDA indication. A recent telephone-based survey of 500 children with allergic rhinitis in the United States found that 28% of parents believed that intranasal steroid sprays were not safe because of the possibility of growth inhibition, a known effect of oral steroid use in children (21). In the past, pediatric studies using budesonide and beclomethasone, first-generation intranasal steroids, showed significant reductions in growth velocity (22, 23). However, second-generation intranasal steroids, including MFNS, exhibit lower systemic bioavailability than first-generation agents and have demonstrated a lack of significant HPA axis suppression, growth impairment, or ocular effects, including cataracts or increased intraocular pressure, in pediatric allergic rhinitis studies after up to 1 yr (11–15, 24, 29).

Few controlled trials have assessed the effects of second-generation intranasal steroids on adrenal suppression at doses higher than those typically used in the treatment of pediatric allergic rhinitis. One study by Agertoft et al. (11) compared MFNS 200 µg vs. budesonide or placebo for 2 wk in 22 children aged 7–12 yr and found no significant differences in lower-leg growth rates measured by knemometry. In a dose-ranging study by Brannan et al. (14), 48 children aged 3–5 yr were given MFNS 50, 100, or 200 µg

Table 3 Treatment-related adverse events reported in > 5% of any treatment group (all randomized patients)

	MFNS 100 µg QD (n = 18)	MFNS 100 µg BID (n = 18)	MFNS 200 µg QD (n = 32)	MFNS 200 µg BID (n = 33)	Placebo (n = 26)	Total (n = 127)
Any AE, n (%)	4 (22)	3 (17)	8 (25)	7 (21)	5 (19)	27 (21)
Headache	3 (17)	2 (11)	1 (3)	3 (9)	2 (8)	11 (9)
Epistaxis	1 (6)	2 (11)	2 (6)	4 (12)	1 (4)	10 (8)
Ear pain	2 (11)	0	1 (3)	1 (3)	0	4 (3)
Pharyngolaryngeal pain	1 (6)	0	1 (3)	1 (3)	1 (4)	4 (3)
Nasal discomfort	0	0	1 (3)	0	2 (8)	3 (2)
Cough	1 (6)	0	0	0	1 (4)	2 (2)
Rhinorrhea	1 (6)	0	1 (3)	0	0	2 (2)
Migraine	0	1 (6)	0	0	0	1 (1)
Diarrhea	1 (6)	0	0	0	0	1 (1)

AE, adverse event; BID, twice daily; MFNS, mometasone furoate nasal spray; QD, once daily.

Table 4 Change in sign/symptom scores, baseline to study end

	MFNS QD (n = 50)	MFNS BID (n = 51)	Placebo (n = 26)
Polyp size			
Baseline	3.34	3.20	3.27
Change at end-point (%)	-0.92 (-26)	-1.10 (-34)	-0.92 (-24)
Congestion			
Baseline	2.12	2.10	2.04
Change at end-point (%)	-0.91 (-38)	-0.99 (-49)	-0.70 (-35)
Rhinorrhea			
Baseline	1.58	1.73	1.63
Change at end-point (%)	-0.70 (-43)	-0.73 (-38)	-0.71 (-42)
Loss of sense of smell			
Baseline	1.09	1.37	1.42
Change at end-point (%)	-0.55 (-49)	-0.53 (-43)	-0.67 (-50)
Therapeutic response			
Score at end-point	1.64	1.25	1.69

BID, twice daily; MFNS, mometasone furoate nasal spray; QD, once daily.

All values are raw (unadjusted) means.

daily for 2 wk; no evidence of an effect on the HPA axis was seen in plasma cortisol response to cosyntropin stimulation in this study.

The recommended dosage of MFNS in adults with nasal polyposis (200 µg twice daily) is twice that recommended for the treatment or prophylaxis of allergic rhinitis (200 µg once daily) (26, 27). Because the dosing of MFNS for patients aged 2–11 yr with allergic rhinitis is 100 µg once daily, experimental dosing for subjects in the present study aged 6–11 yr with nasal polyposis was determined to be 100 µg twice daily. In addition, dosing for patients aged ≥ 12 yr with allergic rhinitis is 200 µg once daily; therefore, the experimental dosing for subjects aged ≥ 12 yr with nasal polyposis was set at 200 µg twice daily.

The primary safety end-point for this study was chosen to address the systemic safety profile of MFNS, because urinary free cortisol is widely accepted as one of the most sensitive methods for determining the integrity of HPA axis function (28). Its measurement has been observed to be more sensitive than morning plasma cortisol to steroid-induced HPA effects and has the advantage of being non-invasive (28, 29). Measurement of 24-h urinary free cortisol integrates an entire day's worth of adrenal gland activity, taking into account the normal daily peaks and valleys of cortisol production (28, 29).

The efficacy data collected in this safety study are descriptive only and are presented without assessment for statistical

significance. The apparent improvements in signs and symptoms seen with MFNS are, however, consistent with data from adequately powered efficacy studies of MFNS in adult nasal polyposis. Two randomized, controlled studies in adult polyposis patients with moderate-to-severe congestion at baseline found that MFNS was associated with significant reductions in polyp size and symptoms (3, 27). Pooled analyses, including 447 patients with nasal polyposis from two adult clinical trials, show that the onset of symptomatic relief with MFNS is rapid; patients receiving MFNS 200 µg twice daily showed significant reductions in rhinorrhea by day 2, congestion by day 3, postnasal drip by day 5, and sense of smell by day 13. Significant improvement in peak nasal inspiratory flow was seen by day 2 (26). The efficacy on MFNS in these trials was accompanied by a low risk of systemic effects; in a dose-ranging study in 967 adults, 21 days of treatment with MFNS was shown to result in no clinically relevant decreases in mean basal or stimulated plasma cortisol level, even at doses up to 400 µg twice daily (30).

A limitation of this study is that it was conducted to evaluate safety, and any conclusions regarding efficacy must be regarded as preliminary. The sparse epidemiologic data for pediatric nasal polyposis indicate the rarity of this condition, with less than 1 per 1000 children in the United States with asthma or allergic rhinitis diagnosed with this disease (6). Although the number of pediatric subjects identified with nasal polyposis in this study was higher in countries outside the United States, the reasons remain unclear, and future studies are necessary to explore this issue.

Conclusions

This study provides evidence of the safety of MFNS in children from 6 to 17 yr of age with nasal polyposis, even at double the pediatric dose used for allergic rhinitis. No clinically meaningful changes were noted in the HPA axis as measured by 24-h urinary free cortisol level, a sensitive indicator of glucocorticoid bioactivity, and effects on HPA. Individual adverse events were generally similar in frequency across the groups, thereby demonstrating the safety of MFNS in children receiving dosages up to 200 µg twice daily. Although this study was not powered for or intended to demonstrate efficacy in pediatric nasal polyposis, the descriptive efficacy data suggest that MFNS may improve signs and symptoms. These findings are consistent with earlier data on the pediatric safety of MFNS and support the safety of its use at higher dosages than previously evaluated in children.

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