

Short-term lower leg growth rate in children with rhinitis treated with intranasal mometasone furoate and budesonide

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Background: Mometasone furoate (MF) aqueous nasal spray is a potent intranasal glucocorticoid with low systemic bioavailability. Knemometry has been shown to be a sensitive method of detecting systemic effects of exogenous steroids in children.

Objective: We sought to assess whether MF (100 or 200 µg) or budesonide intranasal aqueous spray (400 µg) influences the short-term lower leg growth rate in children with seasonal or perennial allergic rhinitis.

Methods: MF, budesonide, and placebo were administered once daily for 2 weeks to 22 children aged 7 to 12 years (mean, 10 years) in a randomized, double-blind, crossover study. Lower leg measurements were done before and after each 2-week treatment period. Two-week washout intervals separated each treatment period.

Results: There were no significant differences in lower leg growth rates among the MF 200 µg (0.95 ± 0.79 mm; mean $\pm$ SD), budesonide 400 µg (0.73 ± 0.61 mm), or placebo (0.69 ± 0.70 mm) groups. The growth rate of the group receiving a 100-µg dose of MF (1.16 ± 0.67 mm) was greater than that for the group receiving placebo ($P = .024$) or budesonide ($P = .033$). No statistically significant sequence effect ($P = .11$), carry-over effect ($P = .24$), overall treatment effect ($P = .086$), or period effect ($P = .065$) was detected.

Conclusion: No short-term adverse effects on linear lower leg growth rates were detected after once daily MF or budesonide at clinically relevant doses. (*J Allergy Clin Immunol* 1999;104:948-52.)

Key words: Children, intranasal steroids, knemometry, growth, systemic effect

The efficacy of orally and nasally inhaled glucocorticosteroids has prompted their widespread use in the treatment of childhood asthma and rhinitis. New products with high topical potency and minimal systemic effects are being introduced, of which mometasone furoate (MF) is the latest example. MF is a synthetic 17-heterocyclic corticosteroid that has a very low oral bioavailability because of both its low rate of absorption from the gastrointestinal tract and its high rate of first-pass hepatic metabolism.¹ MF has recently become available as an

Abbreviation used

MF: Mometasone furoate

aqueous suspension nasal spray formulation for use in the treatment of rhinitis. Pharmacokinetic studies have not been able to detect plasma levels of MF after daily intranasal administration of 50 to 200 µg with an assay that could detect plasma MF levels of 50 pg/L (Schering Plough, data on file). This strongly suggests that intranasal administration of MF will be associated with a low risk of adverse systemic effects, such as growth retardation, which has recently been reported in children treated with intranasal beclomethasone 400 µg/d.²

Knemometry is an established means of measuring the systemic activity of topical steroids in children.³⁻¹⁰ Changes in lower leg length can be measured by the knemometer with an accuracy of 0.1 mm, making the knemometer a powerful tool for investigating the influence of exogenous glucocorticosteroids on short-term linear lower leg growth. This method has also proven useful as a means of comparing the systemic effects of different inhaled corticosteroids or inhalers.^{7,11}

This study used knemometry to determine the influence of once daily treatment with 100 and 200 µg of intranasal MF and 400 µg of budesonide on short-term linear lower leg growth rate in children with perennial, seasonal, or both types of allergic rhinitis.

METHODS

Twelve boys and 10 girls aged 7 to 12 years (mean, 10.1 years) were entered into the study (Table I). All had a clinical diagnosis of allergic seasonal, perennial, or both types of rhinitis for at least 1 year and a verified positive skin prick test response within the preceding year. All children were preadolescent white subjects who were without any signs of puberty (Tanner score, 1). Patients with any nasal structural abnormality, including nasal polyps or marked septal deviation, that significantly interfered with nasal air flow; any atrophic or chronic purulent postnasal drip; or clinical diagnosis of acute or chronic infectious sinusitis were excluded from the study.

All patients had concomitant mild asthma that only required treatment with short-acting inhaled β_2 -agonists as needed. None had received treatment with inhaled or oral glucocorticosteroids during the month before study entry, and no other drugs were taken during the study period except inhaled short-acting β_2 -agonists as needed. Intranasal and ocular steroids were not allowed for 2 weeks,

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TABLE I. Patient characteristics

Boys/girls	12/10
Age (y)	10.1 (7-12)
Height (cm)	141.73 (121-160)
Weight (kg)	38 (23-55)
Seasonal rhinitis (n = 15) duration (y)	4.5 ± 2.56
Perennial rhinitis (n = 7) duration (y)	5.3 ± 2.93

Values given are mean and range or SD.

high-potency dermatologic corticosteroids were not allowed for 1 month, astemizole was not allowed for 3 months, and intramuscular or intra-articular corticosteroids were nor allowed for 3 months before the screening visit.

The study was approved by the local ethics committee, and informed consent was obtained from all children and their parents.

Design

The design was a randomized, placebo-controlled, double-blind, double-dummy, 4-way crossover study. Total study duration was 14 weeks for each patient. After a 3-day run-in period, the children were randomly allocated to a treatment sequence during which each subject received once daily treatment with MF 100 µg, MF 200 µg, budesonide 400 µg, and placebo. Each treatment was given for 2 weeks, separated by 2-week washout periods. The medication was given intranasally as an aqueous suspension pump spray in the form of one spray per nostril of either MF or MF placebo and 2 sprays per nostril of budesonide or budesonide placebo each morning. The sequence of administration (MF and budesonide) was randomized. Each pump spray was primed until an adequate fine mist was observed; this priming procedure was performed just before each treatment period at the clinic while instructing the child and parent in the correct technique for delivery of the spray to the nostrils. The child tilted the head forward and compressed one nostril while the spray was squirted into the other during gently inward breathing through the nostril. The first dose of study medication was administered at the clinic under supervision, and administration technique was checked at each visit.

At all visits, thorough physical and nasal examinations were performed to detect any intercurrent illness or disorder that might interfere with linear growth. Routine laboratory blood tests were also performed.

Measurement of the right lower leg was performed at the beginning and at the end of each of the 4 treatment periods by using a custom-manufactured knemometer. All measurements were performed by the same trained nurse without reference to the recordings made at the previous visit. Measurements were performed at the same time (within ± 1 hour) in the afternoon (between 1 and 8 PM), as recommended for knemometry.¹¹ The children were not allowed to exercise for 2 hours before the visit. After arrival at the clinic, they rested for 10 minutes before their lower leg length was measured 4 times. After resting for another 10 minutes, another set of 4 measurements was made. The most deviant value from each set of 4 measurements was disregarded, and lower leg length on that day was calculated as the mean of the remaining 3 measurements of each set. This mean value of lower leg length was used in the statistical analysis. In addition, height (Harpender stadiometer), body temperature, blood pressure, and pulse rate were recorded.

Intolerable seasonal allergic rhinitis symptoms were treated with loratadine syrup; subjects weighing less than 30 kg used 5 mg, and those weighing 30 kg or more used 10 mg.

The children kept daily records of all medications taken during the trial, including the exact time each nasal spray was adminis-

tered. These records also served as an estimate of compliance with therapy. The occurrence of any adverse events was also registered in the diary cards.

Statistical analysis

The primary outcome measure of the study was the change in linear lower leg growth rate, as assessed by knemometry, from baseline to the end of each of the 4 treatment periods.

Lower leg growth rate was analyzed by using a 4-way crossover ANOVA model, allowing for effects caused by treatment sequence, subjects (within sequence), period, and treatment. On the basis of the least-squares means from the ANOVA model, the following treatment differences were estimated, and 95% confidence intervals were calculated: MF 100 µg/d versus placebo, MF 200 µg/d versus placebo, budesonide 400 µg/d versus placebo, MF 100 µg/d versus MF 200 µg/d, MF 100 µg/d versus budesonide 400 µg/d, MF 200 µg/d versus budesonide 400 µg/d.

Each of the pairwise treatment comparisons was made by using the .05 level of significance and no adjustment for multiple comparisons. Because this was a safety study designed to assess possible treatment effects (relative to placebo) on lower leg growth, it was more conservative to provide unadjusted treatment comparisons in order to maintain the sensitivity of the comparisons of the active treatments with placebo.

The sample size was based on previous research findings by the study investigator, which demonstrated the pooled standard deviation in lower leg growth to be approximately 0.015 mm/d. A total of 20 evaluable subjects would yield a power of approximately 90% to detect a 0.015 mm/d difference.

RESULTS

All 22 randomized children completed the study. The results from one period of one patient was not used in the statistical analysis because his medication expired 4 days before the last visit in the last treatment period (MF 200 µg). All children were preadolescent white subjects with no signs of puberty (Tanner score, 1). The mean duration of seasonal allergic rhinitis was 4.5 years (15 patients) and that of perennial rhinitis was 5.3 years (7 patients; Table I).

The technical error of the knemometer (ie, the mean SD of 3 successive estimations of lower leg length) was 0.07 mm.

No statistically significant sequence effect ($P = .11$), carry-over effect ($P = .24$), overall treatment effect ($P = .086$), or period effect ($P = .065$) was seen. Mean lower leg growth rates during the 4 treatments were 0.35 (placebo), 0.58 (MF 100 µg), 0.48 (MF 200 µg), and 0.37 mm/wk (budesonide 400 µg), respectively (Fig 1). There was no difference between the results in the group of children who took MF first followed by budesonide and those who took budesonide first followed by MF. Marked interindividual differences in growth velocity were observed during all 4 treatments (Fig 1).

Although no overall treatment effect was observed, pairwise comparisons showed statistically significant differences in growth rates between subjects receiving MF 100 µg and budesonide 400 µg ($P = .033$) and between subjects receiving MF 100 µg and placebo ($P = .024$); in both cases lower leg growth was greater after treatment with MF 100 µg (Table II).

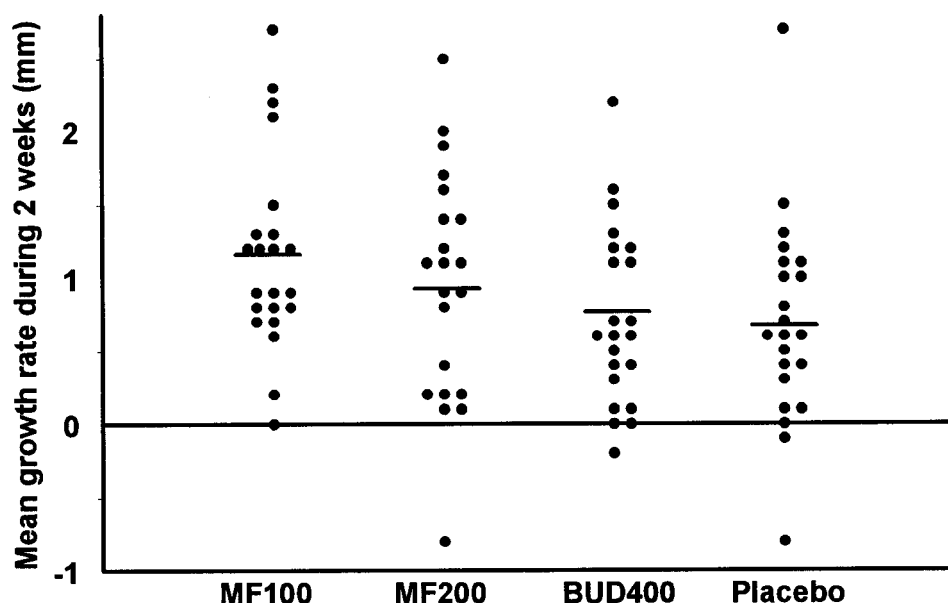


FIG 1. Mean lower leg growth rates during the 4 treatments were 0.35 (placebo), 0.58 (MF 100 μ g), 0.48 (MF 200 μ g), and 0.37 mm/wk (budesonide [BUD] 400 μ g), respectively. Marked interindividual differences in growth velocity were observed during all 4 treatments.

TABLE II. Pairwise comparisons of treatment differences in lower leg growth during 2 weeks

Comparison	Mean difference	95% confidence interval	P value
MF 100 μ g/d vs 200 μ g/d	0.23	-0.17 to 0.63	.260
MF 100 μ g/d vs budesonide 400 μ g/d	0.44	0.04 to 0.83	.033
MF 100 μ g/d vs placebo	0.46	0.06 to 0.86	.024
MF 200 μ g/d vs budesonide 400 μ g/d	0.21	-0.20 to 0.61	.311
MF 200 μ g/d vs placebo	0.23	-0.17 to 0.63	.258
Budesonide 400 μ g/d vs placebo	0.03	-0.37 to 0.42	.901

According to the diary recordings, one child missed 2 doses of study medication during the last 2-week period (MF 100 μ g). The diaries indicated that all other children took their study medication as prescribed during the trial.

All treatments were well tolerated. No subjects discontinued the study because of adverse events, which were observed to occur at similar frequencies during the 4 treatments: 12 children reported an adverse event during treatment with placebo, 10 during treatment with MF 100 μ g, 7 during treatment with MF 200 μ g, and 10 during treatment with budesonide 400 μ g. The most frequently reported adverse events were cough, headache, and pharyngitis. No unusual or unexpected adverse events, abnormal laboratory values, or irregular vital signs were observed.

DISCUSSION

Knemometry has been shown to be a sensitive method for detecting systemic effects of exogenous corticosteroid in the treatment of asthma.³⁻¹¹ Significant dose-response relationships have been found between reduced short-term lower leg growth rate and inhaled corticosteroid dose among children with asthma.^{3-7,11} The

method has been found to be as sensitive as or more sensitive than urinary cortisol excretion in detecting systemic effects or differences in systemic effects between exogenous steroids.⁷ Even low doses of exogenous steroids may have marked effects on short-term lower leg growth rate. For example, daily doses of 2.5 mg of oral prednisolone or 400 μ g of orally inhaled beclomethasone dipropionate entirely stopped lower leg growth over a period of 2 weeks.^{3,5} These treatments are not associated with such a marked and total stunting of long-term growth. Therefore the sensitivity of knemometry seems to make this method more useful for defining doses of inhaled corticosteroids that are unlikely to be associated with any adverse effects on long-term growth rather than predicting the magnitude of long-term growth reduction in patients whose lower legs have been found to grow at a slower rate in a knemometry study.¹¹ This assumption is in good agreement with the findings in some recent growth studies suggesting that the effect of exogenous steroids on growth is more pronounced during the first weeks of the treatment,¹² and hence an adverse effect is more likely to be detected during this period.

Our study consisted of children with allergic rhinitis and concomitant mild asthma because we wanted to min-

imize any possible influence on growth caused by poorly controlled asthma and the possible influence of other medications on short-term lower leg growth. Although inhaled β_2 -agonists have been shown in laboratory studies to reduce the secretion of growth hormone,^{13,14} the children only used this medication very rarely and to the same extent during all periods, and therefore it is unlikely that this treatment influenced the result.

In earlier knemometry studies lower leg length was measured twice a week, and lower leg growth velocity was calculated by assessing the slope of the measurements by linear regression.^{4,6,11,15-17} On the basis of a poststudy analysis performed on the results of these previous studies, we found that the slope assessed by linear regression did not provide any advantages over or result in any conclusions that were different from the *beginning-and-end-of-period* measurement technique, which was used in the present study; the conclusions and the statistical power were similar in all studies. Moreover, the mean SD of 3 successive estimations of lower leg length in this study was 0.07 mm. This is similar to or lower than the values found in our previous studies. Therefore it is unlikely that the lack of detectable adverse effects in this study was due to a lower power than in the earlier studies or a different method of calculating the short-term lower leg growth rates.

Receptor-binding studies have suggested that MF is approximately twice as potent as budesonide.¹ For this reason, we decided to compare a single dose of MF with double the dose of budesonide. Four hundred micrograms of budesonide was chosen because it is the highest recommended dose for this drug and therefore a dose that might serve as a positive control.¹⁸ The lower dose of MF was included because it is a clinically recommended dose. Moreover, a randomized placebo period was included in the comparison to make it easier to adjust for possible period effects, which have sometimes been reported when a knemometry study is being conducted over long periods.³ Finally, we included more patients than in earlier studies to increase the power of the study. Under these conditions, we found none of the treatments were associated with any detectable adverse effect on short-term linear lower leg growth rate. This is in agreement with the results of one study, which found no detectable adverse effects on short-term linear lower leg growth rate by treatment with 400 μ g of intranasal dry powder budesonide given once daily in the morning,¹⁹ but it is in disagreement with the results of another study, which found that 200 μ g of intranasal budesonide administered by means of a pressurized metered-dose inhaler given twice daily was associated with a significant reduction in short-term lower leg growth velocity.¹⁸ These results indirectly suggest that dosing once daily in the morning may be beneficial with respect to minimizing any untoward effects on growth.²⁰⁻²³ Further studies are needed to assess that possibility. The influence of MF on short-term linear lower leg growth velocity has not previously been assessed. The present findings call for further long-term

growth studies with this drug to confirm the lack of adverse effects on growth.

The measured mean lower leg growth velocity during placebo treatment was somewhat lower than the mean reported during the run-in and wash-out periods (around 0.5 mm/wk) in earlier trials of inhaled or oral steroids given to similar patient groups under similar study conditions^{3,6,19,24} but exactly the same as the mean growth rate measured during placebo treatment in another study with a similar number of patients.²⁵ These differences in placebo growth rates from 0.5 to 0.35 mm/wk between different studies are probably due to the spontaneous variations in lower leg growth that have been reported by other researchers,¹¹ differences in growth rates between different groups of children, and different time points of the year when the studies were conducted.^{26,27} It cannot be excluded that the somewhat lower growth rate during placebo treatment in the present study was caused by the time of the year when the study was conducted (mainly October to April, when the growth rate is lower than during the summer period). This emphasizes that comparisons of short-term lower leg growth rates measured during different treatments in different studies or in different groups of children should be made with caution.

The most surprising finding in our study was the increased lower leg growth rate during treatment with MF 100 μ g. We have no explanation for this. In all knemometry studies, including studies of healthy children, outliers and negative values of mean lower leg growth rates have been reported.^{3,5,28-30} In the present study there were no negative outliers, and 4 children had very high growth rates while receiving MF 100 μ g. However, differences in outliers could not alone explain the higher growth rate during treatment with MF 100 μ g (Fig 1). Other possible explanations are as follows.

First, it may be a chance finding. A combination of a growth rate at the lower end of the normal range during placebo and at the upper end of the normal range during treatment with MF 100 μ g may have caused this result rather than a significant increase in growth rate caused by MF 100 μ g. Similar assumptions may also be used to explain the difference between MF 100 μ g and budesonide.

Second, it may be due to an increase in growth rate caused by the MF treatment. This suggestion is supported by the results of a recent growth study, which found that 50 children treated with MF 100 μ g/d intranasally for 1 year grew significantly faster than 50 placebo-treated children (Eric Schenkel, personal communication, 1999). There is no plausible explanation for this possible effect of MF treatment. A certain growth-enhancing effect caused by the molecule itself cannot be ruled out but seems unlikely because it has not been reported with other corticosteroid molecules. If the molecule possessed such growth-enhancing properties, one would have expected an even higher growth rate during treatment with MF 200 μ g. This was not seen. However, it cannot be ruled out that an increase in systemic effect caused by the higher dose of MF may have negated this effect in our study.

Finally, it might be due to an improvement in the clinical condition during MF treatment resulting in better sleep and greater physical activity during daytime with a subsequent positive influence on growth hormone secretion pattern. This mechanism cannot be ruled out in the 1-year study by Schenkel (personal communication). However, it is most unlikely to be playing any role in the present study, which was not set out to compare efficacy between the various treatments. Disease control could only have been an explanation in the 7 children with perennial rhinitis. In the remaining children a substantial number of treatments were administered outside the pollen season, when no clinical improvement would be expected. Finally, similar effects have not been reported with other treatments that have improved the clinical condition.

We do not know which of these explanations or combinations of explanations is the most feasible. We believe that the first explanation is the most plausible. However, more studies are needed to assess our belief.

The children always used 1 dose of MF and 2 doses of budesonide in each nostril. This is a complicated regimen that has a certain risk of medication error. We tried to avoid or reduce this risk by thorough instruction and questioning at each visit. However, because a chronolog was not used in the study to assess compliance, we cannot rule out that some error in the number of puffs taken may have occurred even if the children were thoroughly instructed, well trained, and experienced in participation in clinical trials. The finding that there was no difference between the results in the group of children who took MF first followed by budesonide and those who took budesonide first followed by MF supports our general belief and the recordings in the diaries that showed that compliance was not affected by the double-dummy technique.

Once daily intranasal administration of MF 100 to 200 μ g or budesonide 400 μ g has no detectable adverse effects on the short-term linear lower leg growth rate in children. Long-term growth studies are needed to assess the clinical implications of this.

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