

Knemometric assessment of systemic activity of once daily intranasal dry-powder budesonide in children

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Systemic activity of the intranasal glucocorticosteroid budesonide administered once daily from a dry-powder inhaler (Turbuhaler®) was assessed by knemometry. Lower leg length was measured weekly in 38 children aged 7–15 (mean 11.3) years with allergic or perennial rhinitis. The design was a randomized, double-blind, parallel-group study. After 4 weeks' run-in, the children were allocated to 4 weeks' treatment with either budesonide 200 or 400 µg or placebo. Fourteen children in the budesonide 200-µg group, 13 in the 400-µg group, and 10 in the placebo group completed the study. In the placebo and budesonide 200-µg groups, growth velocities during run-in (0.36 and 0.28 mm/week, respectively) and treatment periods (0.34 and 0.27 mm/week, respectively) were almost identical. In the budesonide 400-µg group (run-in: 0.40 mm/week), a nonsignificant reduction in mean growth velocity of 0.18 mm/week was seen ($P = 0.11$). There were no statistically significant differences among the run-in mean lower leg growth velocities ($F = 1.12$; $P = 0.34$), among growth velocities during treatment ($F = 1.10$; $P = 0.34$), or among the run-in and treatment growth velocities in the three groups ($F = 1.19$; $P = 0.32$). These results provide good evidence that systemic activity is low in children with allergic or perennial rhinitis treated with once daily budesonide in doses of 200- and 400-µg administered intranasally from a dry-powder inhaler.

O. D. Wolthers, S. Pedersen

Department of Paediatrics, Kolding Hospital, Kolding, Denmark

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O. D. Wolthers, MD
Siriusvej 9
DK-8270 Højbjerg
Denmark

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Intranasal application of glucocorticosteroids has been found to be effective in controlling nasal symptoms in children with allergic rhinitis (4). Recent reports, however, have indicated that the systemic activity of intranasal glucocorticosteroids may be more pronounced than previously assumed. Using the knemometer, a new noninvasive device which enables measurement of the length of the lower leg with an accuracy of approximately 0.1 mm (5–7), we detected a marked reduction of short-term lower leg growth velocity in children treated with pressurized, metered-dose aerosol budesonide 200 µg intranasally twice daily (8).

Dry-powder inhalers are currently in clinical development for the treatment of allergic rhinitis in children (1). The aim of the present study was to determine by knemometry whether once daily treatment with intranasal budesonide in doses of 200 and 400 µg delivered from a dry-powder inhaler (Turbuhaler®) has any adverse effect on short-term lower

leg growth in children with allergic and perennial rhinitis.

Patients and methods

Calculation of sample size was performed as described in earlier studies (5–8). Twenty-five boys and 13 girls, aged 7–15 years (mean 11.3 years) entered the study. They were enrolled during the first week of May, i.e., about 4 weeks before the grass pollen season starts in Denmark. All children were outpatients in a secondary referral center. Eight had a history of nonallergic perennial rhinitis of at least 2 years' duration, and 30 had a history of grass-pollen-induced allergic rhinitis of at least 1 year's duration. None had received treatment with glucocorticosteroids for 2 months before the study. Only study-related medications were allowed during the study period. Patient data are shown in Table 1. One child was Asian; the others white. One girl was stage

Table 1. Characteristics of the study groups

	Placebo	Budesonide	
		200 µg	400 µg
Sex			
Male	8	7	10
Female	2*	7*	3**
Age (years)			
Mean	12.0	10.9	11.0
Range	10–14	7–14	7–15
Height (cm)			
Mean	155.7	148.1	145.9
Range	139.0–178.0	128.6–168.5	123.5–164.9
Height standard deviation score			
Mean	+0.53	+0.85	–0.20
Range	–1.49–+2.08	–1.63–+3.29	–2.70–+1.98
Weight (kg)			
Mean	42.9	36.8	38.9
Range	33.5–60.1	24.4–53.6	22.3–56.4
Body surface area (m ²)			
Mean	1.39	1.26	1.27
Range	1.15–1.75	0.94–1.49	0.89–1.61
Duration of allergic rhinitis (years)			
Mean	5	5	5
Range	2–10	1–7	1–10
N	10	10	10
Duration of perennial rhinitis (years)			
Mean	3	3	3
Range	–	2–5	2–5
N	1	4	3

* One girl was Tanner stage III of pubertal development.

** One girl was Tanner stage II of pubertal development.

II and two girls stage III, according to the Tanner rating of puberty. All other children were preadolescents. The study was approved by the local ethics committee, and informed consent was obtained from all children and their parents.

The design was a randomized, double-blind, parallel-group study. After a 4-week run-in period, the children were allocated to a 4-week treatment period with either 200 µg or 400 µg budesonide or placebo. The allocation was performed according to a computerized randomization scheme prepared in balanced blocks.

Dry-powder budesonide was delivered in metered-dose, powder-insufflation devices. Each insufflator contained 200 doses, and each puff delivered either 100 or 200 µg budesonide. Placebo insufflators identical in size and appearance to the active device delivered 100 µg lactose per puff. The dose was one puff in each nostril in the morning. Before the study, the children and their parents received thorough instruction in correct use of the nasal insufflators, so that all demonstrated an efficient technique. Furthermore, insufflator use was checked regularly during the study. Compliance was calculated as the

number of doses taken as a percentage of the expected number of doses taken.

Knemometry measurements and monitoring of symptoms of rhinitis were performed as described in earlier studies (4, 8). Rescue terfenadine tablets were allowed in accordance with previous guidelines (4). The technical error of the knemometer was 0.1 mm.

Lower leg growth velocities were calculated for each period by linear regression analysis and expressed as mm/week. Intragroup comparisons of growth velocities were performed with paired t-test and intergroup comparisons with analysis of variance. The 5% level of significance was used.

Results

Eleven children were allocated to treatment with placebo, 14 to treatment with 200 µg, and 13 to treatment with 400 µg budesonide. One girl with allergic rhinitis was withdrawn from the placebo group at the first visit in the treatment period because she had injured her right leg. The remaining children completed the study according to protocol. The three treatment groups were comparable with respect to the characteristics shown in Table 1, except for the distribution of boys and girls. Compliance with dosage regimen varied from 89% in the placebo group to 111% and 110% in the budesonide 200- and 400-µg groups, respectively (NS). Mean nasal symptom scores and the consumption of terfenadine tablets were uniformly low in all groups during run-in and treatment periods.

Individual lower leg growth velocities are shown in Fig. 1 and mean growth velocities in Table 2. There were no overall statistically significant differences among the run-in mean lower leg growth velocities ($F = 1.12$; $P = 0.34$), among growth velocities during treatment ($F = 1.10$; $P = 0.34$), or among the run-in and treatment growth velocities in the three groups ($F = 1.19$; $P = 0.32$). In the 400-µg budesonide group, mean growth velocity was reduced, with 0.18 mm/week during treatment as compared with run-in (Table 2) ($t = -1.72$; $P = 0.11$). In the two other groups, the mean growth velocities during run-in and treatment were almost identical (Table 2).

Discussion

Short-term knemometry cannot be used to assess or predict statural growth. The method, however, provides a sensitive means of studying the systemic activity of topical glucocorticosteroids in children (5–8). In Denmark, the grass pollen season is of only 3–6 weeks' duration. This makes crossover studies difficult in children with seasonal rhinitis. Therefore, we used an open run-in before the pollen season in combination with double-blind treatment periods.

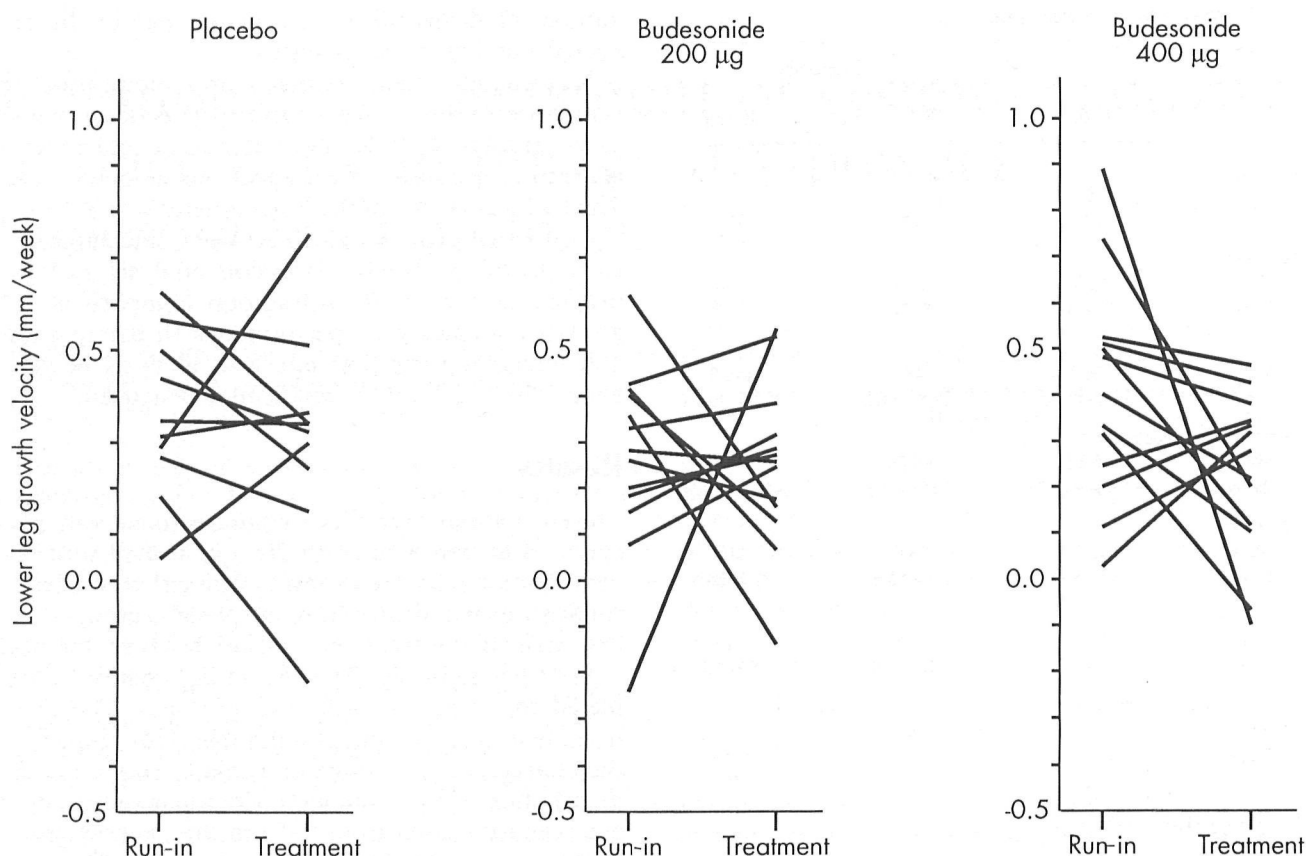


Fig. 1. Individual lower leg growth velocities in placebo group ($n = 10$) and in budesonide dose groups of 200 ($n = 14$) and 400 µg ($n = 13$) during run-in and active treatment.

The finding of almost identical mean lower leg growth velocities during run-in and treatment periods in the placebo group and in the children who received 200 µg budesonide confirms the reproducibility of knemometry. Furthermore, it shows that the results have not been influenced by the lack of blinding during run-in.

Though not statistically significantly, the lower leg growth velocity was reduced during active treatment in the 400-µg group. It cannot be excluded that this

trend would have become significant if we had studied a larger population. In earlier knemometry studies, however, we have found highly significant differences in similar numbers of patients, with standard deviations similar to those in the present study (5–8). In view of this, we believe that treatment of rhinitis in children with 400 µg budesonide once daily from a dry-powder inhaler is associated with less systemic effect than treatment with 200 µg twice daily from a pressurized, metered-dose aerosol (8).

Table 2. Mean lower leg growth velocities and statistical comparisons in children with rhinitis treated with intranasal placebo ($n = 10$), budesonide 200 µg ($n = 14$), or 400 µg ($n = 13$) daily

Treatment group	Mean growth velocity (mm/week (1 SD))		
	Run-in	Treatment	Run-in – treatment
Placebo	0.36 (0.17)	0.34 (0.20)	–0.02
Budesonide 200 µg	0.28 (0.21)	0.27 (0.18)	–0.01
Budesonide 400 µg	0.40 (0.24)	0.22 (0.19)	–0.18
Statistical comparison:			
Budesonide 200 µg and placebo	$F = 0.85$; $P = 0.36$	$F = 0.71$; $P = 0.41$	$F = 0.02$; $P = 0.90$
Budesonide 400 µg and placebo	$F = 0.19$; $P = 0.66$	$F = 2.20$; $P = 0.15$	$F = 1.41$; $P = 0.24$
Budesonide 400 µg and budesonide 200 µg	$F = 2.15$; $P = 0.15$	$F = 0.51$; $P = 0.48$	$F = 2.04$; $P = 0.16$

Several factors may explain this observation. A reduction of dosing frequency is associated with a reduction of the growth-suppressive effect in children treated with glucocorticosteroids (2). The suppression of growth hormone secretion that may be caused by glucocorticosteroids may depend on the time of their administration (3). Morning dosing may be beneficial with respect to reducing the effect on growth.

We do not know whether the antiinflammatory effect of intranasal glucocorticosteroids in children depends on dosing frequency. Although 200 and 400 µg dry-powder budesonide from a Turbuhaler once daily caused a dose-related reduction of nasal symptoms in children (1), the effect of 400 µg appeared to be less impressive than the effect of the same dose administered twice daily from a pressurized, metered-dose aerosol in a comparable population (4). It is not known how various administration forms, inhalation technique, and the distribution pattern of budesonide in the nasal mucosa influence the efficacy and systemic activity in children.

In conclusion, the present study provides good evidence that the risk of important systemic activity is low in children treated with dry-powder budesonide 200 and 400 µg administered intranasally once daily in the morning. Further studies are needed to establish the optimal administration regimen, delivery system, and dose of intranasal budesonide in an effort to combine maximal topical effect with minimal systemic activity.

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References

1. AGERTOFT L, WOLTERS OD, FUGLSANG G, PEDERSEN S. Nasal powder administration of budesonide for seasonal rhinitis in children and adolescents. *Pediatr Allergy Immunol* (in press).
2. BYRON MA, JACKSON J, ANSELL BM. Effect of different corticosteroid regimens on hypothalamic-pituitary-adrenal axis and growth in juvenile chronic arthritis. *J R Soc Med* 1983; 76: 452-7.
3. CASANEUVA FF, BURGUERA B, TOME MA. Depending on the time of administration, dexamethasone potentiates or blocks growth hormone release in man. *Neuroendocrinology* 1990; 51: 46-9.
4. WOLTERS OD, JÖRGENSEN BA, PEDERSEN S. A double-blind, placebo-controlled study of the effect of intranasal budesonide in the treatment of children with seasonal rhinitis. *Acta Paediatr Scand* 1992; 81: 902-6.
5. WOLTERS OD, PEDERSEN S. Growth of asthmatic children during treatment with budesonide: a double blind trial. *BMJ* 1991; 303: 163-5.
6. WOLTERS OD, PEDERSEN S. A controlled study of linear growth in asthmatic children during treatment with inhaled glucocorticosteroids. *Pediatrics* 1992; 89: 839-42.
7. WOLTERS OD, PEDERSEN S. Short-term growth during treatment with inhaled fluticasone propionate and beclomethasone dipropionate. *Arch Dis Child* 1993; 68: 673-6.
8. WOLTERS OD, PEDERSEN S. Short-term growth in children with allergic rhinitis treated with oral antihistamine, depot and intranasal glucocorticosteroids. *Acta Paediatr Scand* (in press).

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