

Systemic Activity of Inhaled Steroids in 1- to 3-Year-Old Children With Asthma

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ABSTRACT. *Objective.* To study the systemic activity of inhaled steroids in young children.

Methods. Forty children with mild asthma aged 1 to 3 years were studied in a 3-way crossover, randomized, placebo-controlled, double-blind trial. Treatment with inhaled fluticasone propionate, 200 μg twice daily delivered via pressurized metered-dose inhaler (pMDI) and Babyhaler (FP400), was compared with budesonide, 200 μg twice daily delivered via pMDI and NebuChamber (BUD400), and to placebo. The Babyhaler was primed before use. Knemometry was used to detect systemic steroid activity. It was performed with a handheld knemometer after 1 and 4 weeks of treatment. The increase in lower-leg length within this 3-week period was used as the outcome measure. The intention-to-treat population was analyzed by analysis of variance.

Results. The increases in the lower-leg length during placebo, BUD400, and FP400 treatments were 85, 45, and 34 $\mu\text{m}/\text{d}$, respectively (adjusted mean). The growth in lower-leg length was significantly reduced from both steroid treatments. The difference between BUD400 and placebo was $-40 \mu\text{m}/\text{d}$ ($n = 25$; 95% confidence interval [CI]: -8 to -72). The difference between FP400 and placebo was $-51 \mu\text{m}/\text{d}$ ($n = 26$; 95% CI: -19 to -83). The difference between FP and BUD was $-11 \mu\text{m}/\text{d}$ and was not statistically significant ($n = 28$; 95% CI: 20 to -42).

Conclusion. FP and BUD are both systemically active in children 1 to 3 years old when administered for 4 weeks from their dedicated spacer devices in daily doses of 400 μg with no difference between the 2 steroid regimens. These findings call for studies of clinical side effects from these treatments of preschool children. *Pediatrics* 2002;109(3). URL: <http://www.pediatrics.org/cgi/content/full/109/3/e40>; inhaled corticosteroid, young child, knemometry, side effects, systemic effects.

ABBREVIATIONS. ICS, inhaled corticosteroids; BUD, budesonide; FP, fluticasone propionate; pMDI, pressurized metered-dose inhaler; RCT, randomized, controlled trial; Plac, placebo.

Inhaled corticosteroids (ICS) are effective treatments for asthma in young children. Budesonide (BUD) and fluticasone propionate (FP) administered from pressurized metered-dose inhalers (pMDIs) and spacer devices have shown beneficial clinical improvements in 0- to 3-year-old children

with asthma in randomized, controlled trials (RCTs) of health outcomes,¹⁻⁴ lung function and bronchial hyperreactivity,⁵ and measurements of the inflammatory marker nitric oxide in exhaled air.⁶ Therefore, the Global Initiative on Asthma International Guidelines recommend using ICS as controller treatment in young children with asthma with persistent symptoms.⁷

Side effects are of concern for any chronic drug therapy in pediatrics, especially ICS.⁸ Recent reassuring data have suggested that long-term treatment of schoolchildren with inhaled BUD for an average of 9 years does not affect final height.⁹ However, some aspects of the assessment of safety are unique to preschool children, including the rapid growth velocity and somewhat different metabolism. The rapid growth in the first 2 to 3 years of life is mainly influenced by factors similar to those that control fetal growth,¹⁰ which may make the child more vulnerable to the adverse effects of drugs and/or disease. Therefore, the safety findings in adults and schoolchildren cannot be extrapolated uncritically to younger children.

Consequently, we decided to study the systemic activity of ICS in younger children. We conducted an RCT on the short-term growth rate as measured by knemometry in children aged 1 to 3 years during treatment with ICS. The primary goal of the study was to investigate the systemic activity of inhaled steroid in the clinically relevant daily dose of 400 μg delivered via dedicated spacers. The secondary goal was to compare the systemic potency of FP pMDI delivered from the Babyhaler (GlaxoSmithKline, Greenford, UK) with BUD pMDI delivered from the NebuChamber (AstraZeneca, Lund, Sweden).

METHODS

Patients

One- to 3-year-old children with a history of recurrent asthma symptoms and currently in a stable condition were included in the study. In the month before inclusion and during the study period, patients were not allowed to take any asthma medication except inhaled β -2 agonists as needed and study medication. Corticosteroids by any route were not allowed. Patients were excluded during the study if they had an asthma exacerbation, defined as needing more than 3 doses of β -2 agonist for more than 3 consecutive days, or if they had a morning temperature above 38°C for more than 3 consecutive days, as these conditions might affect knemometry.¹¹

Study Design

The study was a randomized, double-blind, double-dummy, 3-way crossover study. The patients received, in randomized order, 4 weeks of treatment with BUD, 200 μg twice daily; FP, 200 μg

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twice daily; and placebo (Plac). Informed consent was obtained from the parents.

Medication

BUD was administered as pMDI aerosol suspension of 200 $\mu\text{g}/\text{dose}$ (Pulmicort, AstraZeneca, Lund, Sweden) via NebuChamber spacer as 1 inhalation twice daily. FP was administered as pMDI aerosol suspension of 100 $\mu\text{g}/\text{dose}$ (Flixotide, GlaxoSmithKline, Greenford, UK) via Babyhaler spacer as 2 separate inhalations twice daily. Placebo BUD and placebo FP were administered in a similar manner. Thus, the children had to inhale 2 doses from the Babyhaler (FP or placebo FP) and 1 dose from the NebuChamber (BUD or placebo BUD) each morning and each evening during the 12-week study period. Before each treatment period, the plastic Babyhaler spacers were washed in household detergent, drip-dried, and primed with 10 puffs from a placebo spray.

Knemometry

Knemometry was measured by a hand-held knemometer as previously described (Fig 1).¹² The principle is that of an electronic caliper, which measures the length of the lower leg from above the knee to below the heel. Measurements are performed with the child in a supine position with a 90° flexion in hip, knee, and ankle joints. The 1 fixed cap is held against the knee and the other, adjustable cap is placed under the heel. The 2 caps are parallel, and the distance is continuously measured electronically with a resolution of 10 μm . The investigator's hand stabilizes the knee cap while the heel cap is slowly compressed by the other hand up to a predefined pressure of 80 g, as determined by an interposed spring. At this pressure, a microswitch is activated and the reading is recorded on a computer.

Before knemometry, the child was seated for at least 15 minutes. Knemometry was performed on days 7 and 28 (± 2 days) of each treatment period. For each child, all knemometry measurements were performed by the same observer and at the same time of day (± 1 hour). The observer was blind to the treatment as well as to the previous measurements.

Compliance and adverse events were monitored by having the parents complete a diary each morning and evening regarding use of the study medication, other medication, and any health problem during the previous 12 hours.

Statistical Analysis

Knemometry was performed by taking 5 measurements on each leg. Measurements on both legs were repeated after 15 minutes, and the mean of the 4 medians was calculated and used as the measure of lower-leg length. Short-term lower-leg growth rate was calculated as the mean daily growth during the last 3 weeks of each treatment. The growth rate was calculated as the difference

in lower-leg length after 1 and 3 weeks of treatment divided by the number of days between visits. That is, the first 7 days of each treatment period were excluded as washout between treatments.

The results were analyzed by analysis of variance (SAS 6.12; SAS, Inc, Cary, NC) with subject, period, and treatment as factors. The statistical analysis included all patients who completed at least 1 treatment (intention-to-treat population). Differences in the short-term growth rate between treatments were expressed as adjusted mean differences with 95% confidence intervals.

RESULTS

Patients

Forty children (20 girls) 1 to 3 years of age (mean: 2.4 years) were included in the study, and 25 patients completed all treatments. Exclusions were attributable to noncompliance with study procedures, asthma exacerbations, or exacerbation of eczema requiring treatment with steroid ointments. Twenty-five adverse events were recorded during the study: 9 during Plac, 10 during FP, and 6 during BUD. All adverse events were considered to be common in this age group (airway infections, fever, cough, rash, hoarseness, and hyperactivity) and mild ($n = 21$) or moderate ($n = 4$) with no relation ($n = 18$) or only possibly related to the study medication ($n = 7$). The 7 adverse events that, before unblinding, were considered possibly related to the study medication were hoarseness (BUD 1, Plac 1), facial rash (FP 1, Plac 1), nose bleeding (Plac 2), and sleeping disturbance/hyperactivity (FP 2). In conclusion, the pattern of adverse events was similar in the 3 treatments.

Knemometry

The intention-to-treat group of 40 young children showed a mean short-term lower-leg growth of 85, 45, and 34 $\mu\text{m}/\text{d}$ for Plac, BUD, and FP, respectively (Table 1).

The mean difference (standard deviation) between the first and second median of 5 consecutive measurements on the same leg was 0.12 (1.6) mm. No relation between the difference and the average of the 2 measurements was observed by a scatter plot.

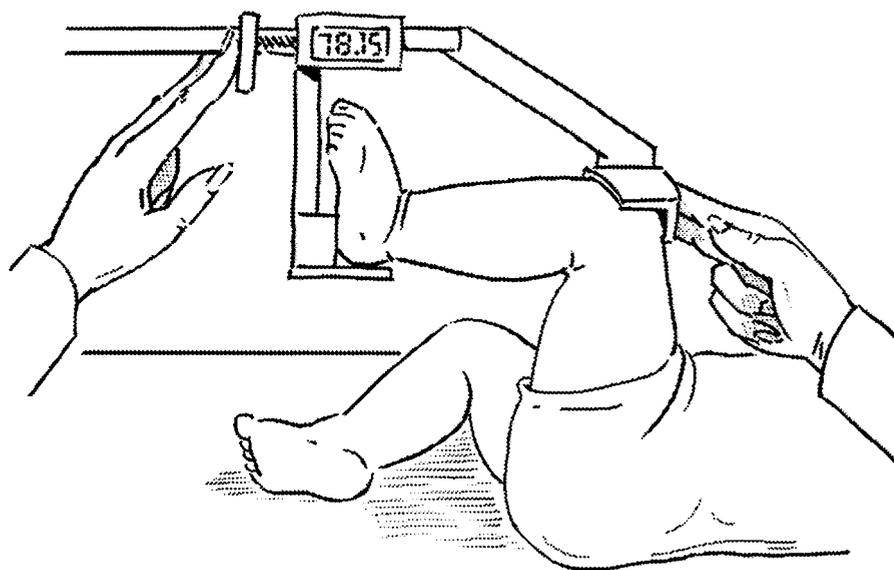


Fig 1. Measurement of lower-leg length with the hand-held knemometer.

TABLE 1. Short-Term Lower-Leg Growth Measured by Knemometry

	Plac	BUD	FP
<i>n</i>	26	28	30
Mean ($\mu\text{m}/\text{d}$)	79	43	33
SD ($\mu\text{m}/\text{d}$)	52	55	57
Adjusted mean* ($\mu\text{m}/\text{d}$)	85	45	34

SD indicates standard deviation.

* Adjusted means are adjusted for subject and period.

There was a significant reduction of the growth rate from either steroid compared with placebo. There was no statistically significant difference in the growth rate between the 2 steroids (Table 2). Individual results are plotted in Fig 2. The analysis was repeated with only those who completed all treatments (per-protocol population) with no effect on the conclusions other than a slight widening of the confidence intervals.

DISCUSSION

This study shows definite systemic activity from the FP 400- μg daily dose inhaled via the dedicated Babyhaler spacer and from the BUD 400- μg daily dose inhaled via the dedicated NebuChamber spacer. The findings are in agreement with our previous RCT on the effect of BUD via spacer in 1- to 2-year-old toddlers¹²: Compared with placebo, 800 μg BUD (but not 200 μg) had a significant effect on knemometry growth rate. The mean growth rate (standard deviation) was 85 (52) $\mu\text{m}/\text{d}$ during the placebo period, which is similar to our previous study in which the mean growth rate was 92 (69) $\mu\text{m}/\text{d}$ during the placebo period.

The finding of systemic activity from both FP and BUD in similar doses is in agreement with a previous pediatric study on knemometry and cortisol excretion in schoolchildren who were treated with BUD 400 $\mu\text{g}/\text{d}$ and FP 400 $\mu\text{g}/\text{d}$, which exhibited similar systemic effects when delivered from dedicated dry powder inhalers.¹³

The decision to study a daily dose of 400 μg ICS was based on observations in clinical efficacy trials in this age group and on recent information on age dependence of lung dose. First, studies documenting the effects of BUD in young children have suggested 400 μg or more as a therapeutically relevant dose.¹⁻³ A dose-dependent effect of FP 100 μg and 200 μg daily was demonstrated without defining the maximum effective dose.⁴ Second, in our recent study on lung deposition of BUD in young children, we showed that lung dose from a fixed nominal dose of aerosol increases with age.¹⁴ This suggests that, from a safety perspective, the prescribed dose of BUD inhaled from a pMDI with a NebuChamber spacer need not be adjusted for age. On the basis of these

TABLE 2. Mean Differences in Short-Term Lower-Leg Growth [95% Confidence Interval] Between Treatments

	Plac-BUD	Plac-FP	BUD-FP
<i>n</i>	25	26	28
Mean ($\mu\text{m}/\text{d}$)	40 [8, 72]	51 [19, 83]	11 [-20, 42]
<i>P</i> value	.015	.002	.491

micrometer / day

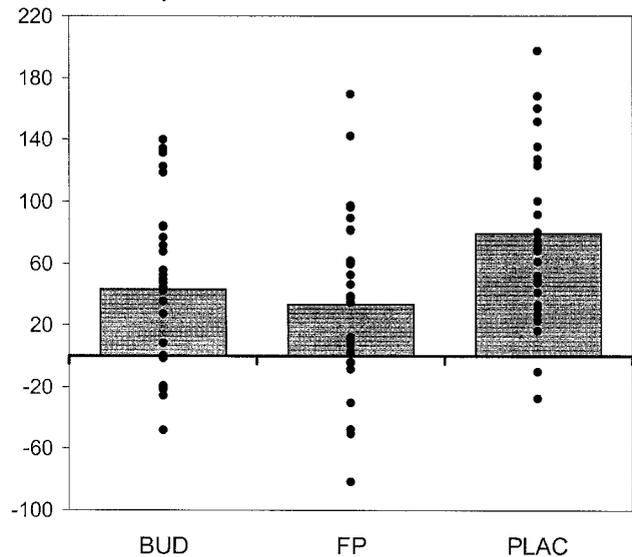


Fig 2. Mean (lines) and individual (circles) short-term lower-leg growth rates during treatment with BUD, FP, and Plac.

observations, we chose to study the safety of a 400- μg daily dose of both ICS.

The systemic activity from FP400 and BUD400 was detected in the present study from a change in short-term growth measured by knemometry. The interpretation of knemometry must distinguish between systemic steroid activity and systemic side effects. Knemometry is currently the most sensitive measure of systemic steroid activity. Any steroid treatment without a detectable effect on knemometry is unlikely to have systemic side effects such as suppression of adrenal function or growth. Conversely, an effect on knemometry is a reflection of systemic steroid activity, which carries a potential risk of systemic side effects. However, an effect on knemometry is not a side effect per se. This short-term measure bears no relation to intermediate- or long-term growth of statural height.^{15,16} Side effects such as adrenal suppression or effects on growth can be studied only through appropriate clinical measurements of adrenal function or height. Our finding of definite systemic steroid activity makes future studies of growth and adrenal function in young children on ICS imperative. FP and BUD delivered via their dedicated spacers showed similar systemic effects at the same nominal dose, but because the efficacy of the 2 treatment regimens (drug and device) has never been compared, a comparison of their therapeutic index cannot be made.

CONCLUSION

FP and BUD administered as pMDI with their dedicated spacers provide similar systemic activity for a similar dose. Both treatments in daily doses of 400 μg produced systemic steroid activity. This suggests the need for clinical trials on possible effects on growth and adrenal function to evaluate the safety implications of this finding, as well as studies on efficacy, so that the true therapeutic ratio of these 2

steroids can be evaluated in young children with asthma.

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