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Lower-leg growth rates in children with asthma during treatment with ciclesonide and fluticasone propionate

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Measurement of short-term lower-leg growth rate in children by knemometry has become established as an integral part of the available measures of systemic activity of inhaled corticosteroids (ICS) in children. The aim of this study was to compare the effects of the novel ICS ciclesonide (CIC) and the ICS fluticasone propionate (FP) on lower-leg growth rate and hypothalamic–pituitary–adrenal-axis function in children with mild asthma. In a double-blind, placebo-controlled, three-period crossover study, 28 children, aged 6–12 yr, sequentially received daily doses of CIC 320 μg, FP 375 μg (330 μg ex-actuator) and placebo via a spacer in a randomized order. Each 2-wk treatment period was followed by a 2-wk washout period. Knemometry was performed at the beginning and end of each treatment period. Cortisol levels in 12-h overnight urine were measured at the end of each treatment period. No statistically significant differences were seen in lower-leg growth rates between CIC (0.30 mm/wk) and placebo (0.43 mm/wk) treatments. Lower-leg growth rate during FP treatment (0.08 mm/wk) was significantly reduced compared with both placebo [least squares (LS) mean: −0.35 (95% CI: −0.53, −0.18; $p = 0.0002$)] and CIC [LS mean: −0.23 (95% CI: −0.05, −0.40; $p = 0.0137$)]. Cortisol levels in 12-h overnight urine were significantly lower in the FP group when compared with CIC ($p < 0.05$); however, there were no statistically significant differences between each of the active treatments and placebo. CIC had no significant effect on lower-leg growth rate in children aged 6–12 yr with mild asthma. In contrast, a similar dose of FP significantly reduced lower-leg growth rate compared with placebo and CIC.

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Due to their high clinical efficacy, inhaled corticosteroids (ICS) are recommended as first-line therapy in children with persistent asthma by international guidelines (1). However, several reports have found that this recommendation is not being followed (1, 2). There seem to be many reasons for this, but undoubtedly the fear of adverse effects of ICS is still an issue for many patients and physicians (2, 3). Therefore, pharmaceutical companies are developing new ICS with high topical potency and lower systemic effects, such as ciclesonide (CIC). Ciclesonide is an almost inactive pro-drug that is converted by esterases in the airways to the pharmacologically active metabolite desisobutyryl-ciclesonide (des-CIC) (4, 5). Studies performed mainly in adults have shown a very low incidence of systemic effects and low concentrations of freely circulating CIC and des-CIC even after inhalation of high doses (6–10). Moreover, due to the low receptor affinity of the parent compound and the high fraction of fine particles delivered by the CIC inhaler, local side effects in the oropharynx, such as candidiasis and hoarseness, are rare (11–14).

All studies investigating the systemic effects of CIC in children have used daily doses of 160 μg or less (11, 15–17), so there is no information about the adverse-effect profile of higher doses in children. By measuring changes in lower-leg length with an accuracy of 0.1 mm, knemometry provides a powerful tool for investigating the influence of exogenous ICS on short-term linear lower-leg growth. In addition, measurement of cortisol excretion in the urine is a sensitive marker of the systemic effects of exogenous steroids (8, 18).

The aim of this study was to compare the systemic effects of daily doses of CIC 320 μg (ex-actuator) and fluticasone propionate (FP) 375 μg (330 μg ex-actuator) by measuring the short-term linear lower-leg growth rate by knemometry, and 12-h overnight urine cortisol excretion, in children with mild asthma.

Methods

Subjects

Outpatient children aged 6–12 yr, without any signs of puberty, and who had: mild persistent asthma for at least 6 months; been treated with only inhaled β_2-agonists as needed for 3 wk prior to the study; and no asthma exacerbation or relevant respiratory tract infection for at least 1 month prior to the study were eligible for inclusion in the study. Also, patients were not to take any other asthma drug during the study period. Girls were classified as pre-pubertal if breasts had elevation of papilla, but no elevation of or enlargement of the areola. Boys were classified as pre-pubertal if testicular volume was ≤ 2 ml as measured with a Prader orchidometer. Apart from asthma and other atopic diseases, the children were healthy. The study was conducted in agreement with the guidelines for good clinical practice, and was approved by the local ethics committee. Informed consent was obtained from all children and their parents before any study-related procedures were undertaken.

Study design

This was a double-blind, double-dummy, placebo-controlled, randomized, three-period cross-over study with a baseline period of 2 wk followed by three treatment periods of 2 wk each. After the run-in period, during which children were familiarized with the study procedures and inhaler use, each child was randomized to receive placebo or CIC 160 μg (ex-actuator) twice daily or FP 250 μg (220 μg ex-actuator) in the morning and 125 μg (110 μg ex-actuator) in the evening. Each treatment period was separated by a 2-wk washout period. Study drugs were administered by a hydrofluoroalkane 134-a metered-dose inhaler (MDI) with a spacer (Aerochamber Plus™, Trudell Medical International, London, Ontario, Canada). All spacers were primed at the clinic just prior to each treatment period. Throughout the entire study, children used inhaled β_2-agonists as needed. No other asthma medication was allowed. The inhalation technique was checked at each visit. Adherence with the treatment was assessed by weighing the canisters before and after each period using a Sartorius BP 3100 S (readability, 0.01 g; linearity 0.02 g). The mean number of puffs used during the treatment period was then calculated. Patients were also asked to enter daily study medication intake in a diary, with, if necessary, help from parents, to enable assessment of compliance.

Assessments

Growth rates. Knemometry of the right lower leg was scheduled at the beginning (treatment baseline) and at the end of each period using a knemometer invented by Valk et al. (19). All measurements were performed at roughly the same time for each individual patient (within 30 min) in the afternoon (between 1 PM and 7 PM) by the same trained operator without reference to the recordings made at the previous visit. The children were measured as recommended for knemometry (20, 21); they were not allowed to exercise for 2 h prior to the visit and had to rest for at least 15 min before the measurements. At each visit, four estimates of lower-leg length were made, the most deviant value was disregarded and the lower-leg length was calculated as the mean of the remaining three measurements and used in the statistical analysis. The technical error of the knemometer (the mean standard deviation of three successive estimations of lower-leg length) was 0.07 mm. For each patient, the growth velocity between each measurement was calculated using the following formula: LLL_1[mm] − $LLL_{baseline}$[mm]/time[week], where LLL_1 = last measurement of lower-leg length and $LLL_{baseline}$ = baseline measurement of lower-leg length for a particular treatment period. In addition, height (Harpenden stadiometer; Harpenden Ltd, Crymych, UK) and weight (electronic beam analyzer) were recorded.

Cortisol levels. At the end of each treatment period, overnight 12-h urine samples were

collected for analysis of urine cortisol, which was measured by a high-performance liquid chromatography method with an intra-assay coefficient of variation of $\leq 5.8\%$. Only cortisol measurements from patients who were treated with study medications as intended were included in the analysis.

Physical examinations and adverse events. A complete physical examination, including blood biochemistry and hematology laboratory values, was carried out at enrollment and at the end of the final treatment period to detect any illness or disorder that might interfere with linear growth. If a fungal infection of the mouth or throat was suspected, a culture was taken and sent to the laboratory for confirmation of the diagnosis.

Pulmonary function. At each visit, forced expiratory volume in 1 s (FEV_1) was measured according to American Thoracic Society recommendations. Throughout the study, peak expiratory flow (PEF) rate was measured at home in the morning and evening [best of three efforts with an Astech peak flow meter (Center Laboratory, Port Washington, NY, USA)]. In addition, the use of rescue medication (inhaled β_2-agonists) and asthma symptoms during the night and day were recorded in diaries. Asthma symptom scores were based on a 5-point scale.

Statistical analysis

The sample size consideration of 28 patients (n = 24 completers) was determined on the grounds of the findings in earlier knemometry studies (22). No power calculation was carried out for study planning. The full analysis set was used to describe the analysis set that was as close as possible to the intention-to-treat patient population, which included all randomized patients who had taken at least one dose of each study medication. In addition, a robust intention-to-treat analysis was used, where two patients each had one treatment period excluded because of protocol violations. A per-protocol analysis was also carried out, which consisted of all patients who had no major protocol violation. Any decision to exclude patients from the per-protocol analysis was made before the data were unblinded and fully documented. Growth velocities of the lower leg were calculated for each period as the difference between the value at the end of each period (end-point) and the corresponding value at the start of the period, and expressed as mm/wk. The analysis of covariance model for the three-period crossover design included the fixed factors of treatment, sex, period and treatment sequence, and the baseline length of the lower leg at each period, as well as body weight as covariates. Furthermore, the nested factor 'patient within sequence' was included in the model as a random effect. The analogous model used to investigate cortisol variables included the fixed factors treatment, period, sex, treatment sequence and the random nested factor 'patient within sequence'. The overall level of significance was set to 5%, two-sided. As no interaction term was included in all the models, the type III sum of squares was used for all analyses. Spirometry FEV_1, diary variables and further safety and efficacy variables were analyzed descriptively.

Results

Demographics

Fifteen girls and 13 boys aged 6–12 yr (mean: 10 yr) were included in the study (Table 1); all were prepubertal. All patients completed the study. One treatment period for two patients (two treatment periods in total) were excluded from the robust intention-to-treat analysis due to protocol violations [one due to wrong use of study medication in period three (treatment sequence CIC/placebo/FP), the other due to a technical problem with the knemometer during the placebo period – the knemometer's measuring plateau counterweighted pulley malfunctioned, thereby, restricting movement]. The children had mild asthma ($FEV_1 \geq 90\%$) and the mean percent predicted FEV_1 was 93.5% for placebo, 92.2% for CIC and 92.4% for FP. Compliance with therapy was high. Based on diary recordings, mean compliance was ≥95% in all treatment periods. When based on the weight of the canisters before and after each treatment period, mean compliance was 102.7% (range: 40.8–134.7%) with CIC and 95.7% (range 57.7–112.5%) with FP.

Table 1. Demographic data for the intention-to-treat population at baseline

Patients (n = 28)	
Age (years), median (range)	10 (6–12)
Sex, n (female/male)	15/13
Height (cm), mean ± s.d.	139.0 ± 9.4
Weight (kg), mean ± s.d.	34.1 ± 8.4
Duration of asthma (months), mean ± s.d.	87.9 ± 33.6
FEV_1 (% of predicted) , mean ± s.d.	93.0 ± 7.3

FEV_1, forced expiratory volume in 1 s; s.d., standard deviation.
FEV_1 values are from the start of the first treatment period.

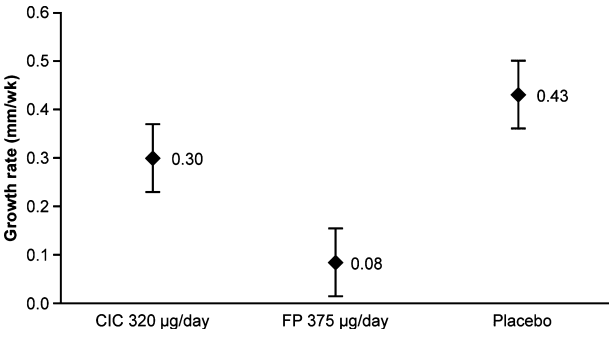

Fig. 1. Effect of ciclesonide (CIC) and fluticasone propionate (FP) on lower-leg growth rate in the intention-to-treat analysis. Data are presented as least squares mean ± standard error of the mean. CIC 320 µg/day, n = 28; FP 375 µg/day, n = 27; placebo, n = 27.

Assessments

Growth rates. Lower-leg growth rates [least squares (LS) means] in the intention-to-treat robustness analysis (i.e., that excluding the invalid data from the protocol violations) during the three treatments were 0.43 mm/wk (placebo), 0.30 mm/wk (CIC) and 0.08 mm/wk (FP) (Fig. 1). Lower-leg growth rate with FP treatment was significantly lower than the growth rate with placebo (LS mean: −0.35 [95% CI: −0.53, −0.18; p = 0.0002) treatment. The lower growth rate with CIC treatment was not significantly different than that seen with placebo treatment (p = 0.15). The growth rate with CIC was significantly higher than that with FP [LS mean: 0.23 (95% CI: 0.05, 0.40; p = 0.014)]. An analysis including the invalid data for the protocol violations confirmed the findings of the robustness analysis.

Cortisol levels. Results from the 12-h urine cortisol analyses are shown in Table 2. No statistically significant differences were seen between either of the active treatments and placebo. However, the cortisol levels were significantly higher during treatment with CIC (51.9 nmol/l) than during treatment with FP (33.4 nmol/l).

Physical examinations and adverse events. Eighteen children experienced 32 adverse events (AEs) during the treatment periods: seven experienced 10 AEs during CIC treatment, seven experienced seven AEs during FP treatment, and 11 experienced 15 AEs when receiving placebo. The most frequently reported AE was nasopharyngitis. Few severe AEs were seen: headache (n = 1, CIC), upper abdominal pains (n = 1, FP), influenza-like symptoms (n = 1, FP), nasopharyngitis (n = 1, placebo) and cough (n = 1, placebo). There were no AEs related to blood biochemistry and hematology laboratory values.

Pulmonary function. There were no clinically relevant changes in asthma control during the study based on home diary recordings, including morning and evening PEF, asthma symptom score and rescue medication use (data not presented).

Discussion

Efficacy studies have suggested that µg for µg, CIC and FP are equally effective in children (11, 23) as well as in adults (12, 24, 25). Therefore, we compared the systemic effects of the same doses of the two drugs delivered from the same spacer system in pre-pubertal children. With the double-dummy design of the study, twice-daily dosing was also clinically more feasible. Furthermore, the randomized placebo treatment ensured that the comparison took place on the steep part of the lower-leg growth suppressive dose–response curve (26). Under these conditions, it was also found that 2 wk of treatment with daily doses of CIC 320 µg was associated with significantly less negative impact on lower-leg growth rate and overnight cortisol excretion in the urine than a similar dose of FP, indicating that the systemic effects of these two drugs are different. It is important to note, however, that the long-term clinical relevance of these differences remains unknown. Other short-term studies have found similar effects of some ICS on lower-leg growth rates (22, 27–29). Moreover, the results from the present study are in agreement with the findings of other studies assessing the systemic effects of CIC and FP as determined by measuring plasma

Table 2. Overnight (12-h) urine cortisol values

Test	Urine cortisol, nmol/l	Reference	Urine cortisol, nmol/l	Difference, nmol/l	95% CI	p-value
CIC 320 µg/day (n = 26)	51.9 ± 6.5	FP 375 µg/day (n = 27)	33.4 ± 6.4	18.4 ± 7.8	2.8, 34.1	0.022
CIC 320 µg/day (n = 26)	51.9 ± 6.5	Placebo (n = 25)	43.0 ± 6.7	8.9 ± 8.0	−7.2, 24.9	0.27
FP 375 µg/day (n = 27)	33.4 ± 6.4	Placebo (n = 25)	43.0 ± 6.7	−9.6 ± 7.9	−25.5, 6.3	0.23

Data are presented as least squares mean ± standard error of the mean. CIC 320 µg/day, n = 26; FP 375 µg/day, n = 27; placebo, n = 25. CI, confidence interval; CIC, ciclesonide; FP, fluticasone propionate.

cortisol levels or urine cortisol excretion in adults (6–9).

Clinical dose-response has been demonstrated for some outcomes with daily CIC doses up to 160 μg in children (15, 17, 23). Therefore, doses up to 160 μg constitute the normally recommended dose range in this patient group. An earlier knemometry study found no impairment of lower-leg growth rate or urine cortisol excretion of CIC doses in this dose range (15). However, some children with asthma may require higher daily doses to obtain better control of some outcomes, such as bronchial hyperresponsiveness or airway inflammation. Therefore, it is also clinically relevant to assess the effects of a daily dose of CIC 320 μg on lower-leg growth rate, as the adverse effects of such doses have not previously been assessed in children. The observed lower-leg growth velocities during CIC and placebo treatments in the present study were in good agreement with expected velocities reported in the earlier trial (15); lower-leg growth rates with placebo treatment were 0.43 and 0.41 mm/wk in the present and former studies, respectively. In the former study, the growth rates during CIC treatment were 0.43 mm/wk (CIC 40 μg), 0.40 mm/wk (CIC 80 μg) and 0.37 mm/wk (CIC 160 μg) compared with 0.30 mm/wk (CIC 320 μg) in the current study. The three lowest doses were administered by pressurized MDI directly, whereas the 320 μg dose was administered by a spacer, to ensure maximal exposure to CIC. It is not possible to determine how the different devices in the two ciclesonide studies may have affected the lower-leg growth rates. In order to determine this, another study in which both devices are used would be required. As different devices deliver different amounts of drug to the lungs it would be expected that the same drug delivered by two different devices could sometimes result in different systemic effects. Therefore, the same delivery system was used for the two drugs in the present study.

It is important to note that a lack of systemic effects may be due to poor compliance with study medication, and that any difference in systemic effects between various treatments may be due to differences in compliance. Adherence to therapy is difficult to assess, therefore in the current study we used both diary recordings and weighing of the canisters before and after each treatment period. The weighing of canisters accurately reflects the number of doses actuated. However, it cannot be ruled out that not all doses have actually been inhaled. As the patients were unaware of the weighing of the canisters, they had no incentive to try to keep an account of how many doses they should have taken and then actuate the inhaler that number of times. This would have been quite complex to achieve as a different number of puffs had to be taken from the two inhalers used. Similar compliance rates were found during all three treatment periods using the two methods, making it unlikely that the differences found between treatments in the study would be due to differences in compliance.

Generally, the results from overnight cortisol excretion in the urine corroborated the finding of the knemometry; patients treated with FP had significantly lower levels of cortisol than those treated with CIC. However, in contrast to the knemometry findings, neither of the active treatments had a statistically significant adverse effect on urine cortisol levels compared with placebo. The reason for this is not clear, but previous studies investigating the effects of ICS have rarely indicated a correlation between knemometry findings or statural growth rates and changes in urinary cortisol excretion levels (22, 27). Furthermore, knemometry has been shown to be a very sensitive technique for detecting systemic effects of different exogenous steroids (22, 28, 30–32), and may be more sensitive than measurements of urinary cortisol excretion in this respect.

Findings from a previous study investigating the effects of CIC and FP in adults on the HPA axis have shown that changes in 24-h urinary free cortisol were similar to changes in serum cortisol levels (8), suggesting that urinary free cortisol can be used as an indicator of HPA-axis function. In this study, overnight urine cortisol excretion was chosen because it was deemed that compliance for a shorter collection period would be much higher compared with a 24-h period. Furthermore, the effects of the study medication on the HPA axis were assessed with overnight urine cortisol measurements, which have been shown to be as sensitive as the respective measurements from 24-h urine collections (18). As urine samples were collected over 12 h, we did not correct the urine cortisol values for creatinine excretion because there is little information about the normal range for, or circadian rhythms of, either urine creatinine or cortisol excretion in the age group studied.

Statistically significant reductions in lower-leg growth rates have always been seen in knemometry studies with ICS doses that affect 1-yr statural growth (26). Furthermore, the method is so sensitive that low doses of exogenous corticosteroid that do not adversely affect

statural growth over 1 yr have sometimes been found to significantly reduce short-term growth rate as measured by knemometry (26). Therefore, knemometry seems to be useful for defining those ICS doses that are unlikely to be associated with any adverse effects on growth in the long-term (26), rather than predicting effects on long-term growth or attained adult height. Consequently, the present findings suggest that long-term treatment with daily doses of CIC 320 μg are unlikely to be associated with any clinically important adverse effects on long-term growth in height.

Assessments of PEF, FEV_1, symptom scores and rescue medication use were done to ensure adequate asthma control during the study, as loss of asthma control may influence growth rate (26, 33). These outcomes were assessed using descriptive statistics; no further statistical analysis was carried out on these outcomes as the sample size was small and all patients who were enrolled had mild asthma.

In conclusion, in children aged 6–12 yr with mild asthma, treatment with CIC 320 μg/day was associated with fewer adverse systemic effects on lower-leg growth rate and urine cortisol excretion than a similar daily dose of fluticasone propionate.

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