

Review Article

Methodology and implications of knemometry in growth assessment of inhaled glucocorticoids

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When validated recommendations for standardization and measurement procedures are used short-term assessment of lower leg growth by knemometry is a highly accurate and reproducible method for assessment of systemic activity of inhaled glucocorticoids. Crossover and parallel designs applying consistent measurement intervals can be used. Crossover designs with a single-blind run in and washout and double-blind active periods are as sensitive as designs using randomized placebo periods. In populations of children, short-term knemometry appears to be capable of defining specific glucocorticoids, application devices and doses that do not suppress long-term height growth. Although no specific cut-off level can be identified in individuals from the available randomized, double-blind short-term knemometry and intermediate-term height growth rate studies, good evidence have been provided that if the short-term lower leg growth suppression in populations of children is higher than approximately 25%, the risk of intermediate-term growth suppression becomes significant with a mean height growth rate retardation in the range of approximately 0.5–1.5 cm during the first year of treatment. Short-term knemometry should be performed as an integral part of the safety assessments of new inhaled glucocorticoids and inhalation devices in children with asthma, before intermediate-term height growth evaluations are initiated.

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The knemometer, derived from the Greek word η $\kappa\nu\eta\mu\eta$: the lower leg, was first introduced in auxology in 1983 (1). With reference to the inventor, the device was to become known as the Valk knemometer. In 1988, an evaluation of basic methodological aspects of short-term knemometry was published (2), and a couple of years later the first randomized double-blind trial of growth effects of exogenous glucocorticoids was presented (3), followed by a series of clinical trials of intranasal and inhaled glucocorticoids (4–7). In 1997, we preliminarily reviewed methodological conditions for short-term knemometry when used for growth assessments of glucocorticoid treatment (8). During the past

decade, an extensive amount of knemometry and long-term randomized, double-blind growth data on inhaled glucocorticoids have increased our knowledge of strengths and weaknesses of short-term knemometry. The present paper aims to review our current knowledge of important methodological aspects and implications of short-term knemometry in children with asthma treated with inhaled glucocorticoids.

The knemometer

The knemometer was constructed for measuring of the distance between the surface of the knee and the heel of the right or left leg of the sitting

child (1). The distance, by definition *the lower leg length*, incorporates the two main components, bone and soft tissue: the length of the tibia, the joint of the knee, the width of the distal femur, the ankle joint and all soft tissues covering the heel and the knee, as well as talus, calcaneus and parts of the foot. Over the years the prototype produced by Valk has been improved. The modified Valk knemometer that we have been working with during the past decade (Fig. 1) was modified based on our experience from measuring extensive populations of children in clinical trials. The knemometer can be used in children from the age of 5 yr.

The knemometer consists of two main parts situated on two separate rigid metal frames. The anterior frame holds the footplate, the measuring ruler and the measuring plateau. The posterior holds an adjustable chair, which is supported by a chair frame that moves on frictionless rollers on a track on the base of the frame. The electronic ruler with a measurement interval of 0.1 mm is attached to a horizontal Perspex plateau by lightweight wiring. The measuring plateau is free to move vertically and easily by means of a counter-weighted pulley. The counterweight is



Fig. 1. A child sitting in measurement position in the knemometer.

held within a Perspex tube supported by the anterior frame and is adjusted to exactly balance the plateau and wiring. The ruler is calibrated at the start of each day, by moving the measuring plateau to a fixed plateau 26 cm above the footplate. The footplate has a rectangular low frame of plastic to hold a piece of paper (the foot template). The chair may be adjusted for each individual's height by means of wheel and ratchet systems, the suitable settings being recorded on a scale on the lateral side of the chair back, and on a scale on the chair track on the base of the posterior frame. The chair back may be placed in different positions allowing for three possible chair depths.

To take a measurement, the child dressed in underwear is placed on the chair with his bottom in the middle of the seat and the spine centered on the chair back. The seat depth is adjusted so that the child feels comfortable. The height of the chair is set so that the leg is flexed to less than 90° with the feet resting on the footplate and the chair brought forwards. Once the seat has been adjusted foot templates are drawn with the feet comfortably positioned consistent with the upper leg. Finally, the chair is rolled into a starting position with the leg flexed to somewhat less than 90° , and the starting position is recorded again from the scale on the chair track. In summary, the information required for each individual that is measured for the first time is seat depth, chair height, the starting position, and foot templates must be drawn. The settings, which are all recorded in the foot templates, require some 15 min of trial and error adjustment to find the most comfortable and suitable positioning. Once determined the settings specify the measuring conditions for the individual child, and the knemometer is pre-set at the conditions before subsequent measurements.

Having defined measurement conditions, to take a measurement, the child is asked to place himself in the knemometer with his feet within the outlines of the foot templates. The measuring plateau is brought down to rest gently on the upper part of the knee. The movements of the knee below the measuring plateau are smoothed by the use of a skin powder. The child must be observed to be content and relaxed. The arms should be crossed and held in front of the body to avoid any pressure on the legs. The auxologist then moves the seat forwards and backwards by turning the relevant wheel until a maximum reading of length is obtained, and simultaneously moves the leg medially and laterally by gentle pressure on the upper thigh until a stable reading is obtained and recorded. The chair is then

moved back to allow the child to dismount and walk a few steps before a second measurement is taken.

On the basis of rigorous evaluations, four independent estimations of the lower leg are taken in each measurement session, the first one being discarded and the following three averaged for the actual lower leg length determination (2). Using the four-estimation technique in studies of short-term growth in children treated with exogenous glucocorticoids, the technical error of knemometry has consistently been found to be in the range of 0.07–0.13 mm (4–6). With respect to accuracy, nothing seems to be gained from using more than four estimations or from discarding the most deviant value of four estimations (9, 10).

When the children are consistently positioned at each measurement, trained observers may substitute for each others in clinical trials of exogenous glucocorticoids without jeopardizing accuracy. The variation between two experienced observers relative to lower leg length was 0.08%, in a series of double measurements, in a population of healthy children (11).

Steps should be taken to minimize non-growth influences, on the lower leg such as diurnal variations, physical activity and variations in weight and hydration during clinical trials (2). That can quite easily be achieved by measuring the individual child at the same time of the afternoon and on the same day of the week. Dehydration and weight loss are significant confounders of knemometric growth rates. Protocols need to specify that major surgery requiring general anesthesia or febrile illness with temperature $>39^{\circ}\text{C}$ for more than five consecutive days within a week, before a scheduled knemometry session should lead to withdrawal from the study.

Variations in pulmonary function

There are no indications from the available knemometry studies that variations in pulmonary function may be associated with variations in short-term growth rates. Minor to moderate decreases in pulmonary function (<25 to 30%) have often been detected during treatment with inhaled glucocorticoids or during placebo periods without associated variations in growth rates (3, 4, 7, 12–19). Short-term growth data from study periods, during which reduced pulmonary function is detected, need only be excluded from analysis if the condition may be severe enough to cause significant variations in hydration or physical activity.

Short-term growth variations and soft tissue effects

Even when systematic influences on lower leg length measurements such as diurnal variations, physical activity, and spontaneous changes in weight are controlled for a day-to-day variation of up to 1.5 mm have been found in healthy children (2). The cause of the day-to-day variation has been suggested due to soft tissue changes. Slight dehydration, changes in physical activity during the day, and different degrees of loading of the knee immediately prior to measuring may explain some of the variability. In randomized studies of exogenous glucocorticoids unexplained positive variations in lower leg length have been more frequently reported than negative variations. Also, positive variations of up to more than 3 mm/wk have been more marked than negative ones that have been as low as -0.6 mm/wk (3, 4, 7), except for one that was around -0.90 mm/wk (9). Such extreme variations have only been found in trials using twice weekly measurements, whereas in trials using measurements at 1, 2 and 4 wk knemometry intervals in prepubertal children, the mean growth rate variations have been in the range of approximately 0.90 and -0.05 mm/wk (9–14). The impact of outliers on mean growth rate assessments is more severe when more frequently lower leg length is measured and the shorter the observation periods are, whereas it is reduced when less frequent measurements are taken and the periods are longer. To some extent that may explain why we have seen no severe mean growth rate outliers in our recent series of studies in which measurements have been taken every second or third week (17, 18, 20). Only one study, which used twice weekly measurements, found that outliers influenced statistical test results of the growth results (9). In the study, one outlier was found during active (approximately -0.90 mm/wk) and one during placebo treatment (approximately $+1.30$ mm/wk). When the outliers were included in data analysis, the observed mean group growth rates of 0.30 during active and 0.52 mm/wk during placebo differed statistically significantly. When they were excluded, the rates of 0.36 and 0.49 mm/wk, respectively, did not differ statistically significantly. In clinical studies, growth rate outliers probably represent a variation which may be caused by postural soft tissue influences due to variations in the time at which the children get out of bed in the morning. To minimize the influence of outliers on the growth results of randomized group studies in prepubescent children, protocols need to specify that period based

growth rates outside the range from -0.10 to 1.00 mm/wk should be excluded from analysis.

Short-term lower leg growth suppression and dose-related suppression of the serum marker of type III collagen, the amino terminal of type III procollagen, were found in children treated with prednisolone 2.5 and 5 mg prednisolone or inhaled budesonide 200, 400 and 800 μ g inhaled budesonide/day (3, 4, 21, 22). That was taken to suggest suppressive effects on type III collagen which is present in the soft tissues of the lower leg. Furthermore, in children treated with systemic glucocorticoids, numerical reductions in lower leg length have been seen during approximately the first three treatment days, whereafter the length increases at a suppressed rate (3, 5). Such observations were explained by de-swelling effects in the soft-tissue component in the lower leg length. A 1-wk randomized crossover trial found prednisolone 5 mg/day to reduce subcutis over the knee by 0.28 mm showing that some, although not all, of the reduced suppression of short-term lower leg growth due to exogenous glucocorticoids may be accounted for by soft-tissue effects (16). Occasionally, inhaled glucocorticoids have been found to be associated with numerical reductions in leg length at the first measurement, after the treatment was initiated (4, 7, 16). In group studies of inhaled glucocorticoids, however, such observations have been found not to influence population based results.

To reduce possible influences from spontaneous growth rate variations and soft tissue effects the child and the parents should be instructed that the child must not participate in heavy exercise 3 h prior to the visit at the centre. Five minutes prior to the measurements, the child should rest in a chair. The child should be dressed in underwear. Though there are no robust data for verification in children participating in short-term studies, it is convention that the measurements should be taken between 1 and 7 PM to reduce influences of diurnal variations.

Growth rate calculation

To reduce confounding of spontaneous variations in lower leg growth, it was first suggested that five measurements at a constant interval should be performed during short-term observation periods 2 or 4 wk or longer (23, 24). All measurements were recommended to be included in the calculation of growth rates by fitting a regression line to the measurements, and the growth rate was calculated as the slope of the regression line and was expressed as millimeter per week. We adopted the linear regression

method based on twice-weekly measurements in our first studies of exogenous glucocorticoids, however, soon became aware that the huge number of visits to our laboratory represented a significant hindrance to children's consent to participation in knemometry studies. The typical number of visits was in the range of 24–36 during a 3 or 4 months period. Therefore, we decided to challenge the linear regression method for growth rate assessment. In three studies, the conventional method for calculation of longitudinal growth, which is based on the perception of growth being a difference in length divided by the time interval between two measurements, was compared with the linear regression analysis method (25). Glucocorticoid treatment periods of 2 and 4 wk, applying once-weekly or twice-weekly measurements, were assessed. Mean growth rates and results of significance tests based on the two calculation methods were similar in all studies, and highly statistically significant coefficients of correlation in the range of 0.81 to 0.97 were found. So, when glucocorticoid periods of 2 and 4 wk were assessed, one measurement at the first and last day of each period produced reliable lower leg growth assessments. Subsequent knemometry studies have applied the conventional method for the calculation of growth rate.

Study design

Randomized, double-blind crossover and parallel designs applying consistent measurement intervals can be used for short-term knemometry in populations treated with inhaled glucocorticoids. Confounding influences on the growth results from possible inter-group differences in spontaneous growth rates may be reduced in the crossover design. Crossover designs with a single-blind run in and washout and double-blind active periods are as sensitive as designs using randomized placebo periods. A single-blind run in gives an opportunity for the participating children to become acquainted with new inhalation devices and techniques, that may increase compliance during active treatments. The application of randomized placebo periods for comparisons of more than one active treatment tends to increase the duration of the study. Concerns about study duration and possible period effects have led to the use of parallel group trials, with intra-group comparisons of active treatment with placebo (19, 20). The advantage of the design is that the total study duration time can be reduced, however, that may be at the cost of a reduction in sensitivity, which may cause difficulties in

interpreting the results (9). Such problems are avoided by using the three-period trial with a single-blind run in or a double-blind placebo. One such trial found a period effect, however, more recent trials using identical protocols did not find period effects (7, 17, 18). As long as the individual child completes the study in less than 4 months, the total duration of enrolment of the whole study population does not affect the results (20). In children, with mild asthma treatment, free run in and washouts are possible. For ethical reasons, treatment free periods are often not possible in children with moderate and severe asthma. In such populations, crossover designs, using four to eight periods of which the first 1 or 2 wk are discarded from analysis can be used to avoid any carry over effects on the growth effects (15). None of the available randomized, double-blind two or three periods crossover trials which used 1 or 2 wk washout periods has reported carry over effects. An analysis of the duration of short-term growth suppression, after withdrawal of exogenous glucocorticoids found good evidence that a 1 wk washout allows for full recovery of suppressed short-term lower leg growth rates (26). Finally, protocols should specify that the measurements should be taken within ± 3 to 4 days of the scheduled intervals.

Sample size

In healthy children, the standard deviation of the mean growth rate of the lower leg was reported to be approximately 0.20 mm/wk (2, 23). In accord with that power calculations showed that 12 children would be enough to achieve a power of > 0.90 in detecting a 50% growth reduction (4, 5). Several studies in children with asthma and allergic rhinitis, however, have shown that the estimation of the standard deviation for mean growth rate of the lower leg of 0.20 mm/wk may be too conservative. The standard deviation of mean lower leg growth rates has often been found to be around 0.30 mm/wk (5–7, 12). Importantly, when an effect size of 50% is used non-statistically significant results do not rule out that effects smaller than 50% may occur or, indeed, that such effects may be clinically important. Rejection of the null hypothesis only implies that the detectable effect would be 50% or more. If the null hypothesis is that there is no effect on short-term growth an equivalence study demonstrating that the comparative (placebo or active) and active treatment periods are equivalent may be applied (27). As a short-term knemometry trial of inhaled glucocorticoids essentially is a safety study equivalent studies should aim at

establishing non-inferiority (28). A power calculation based on the standard deviation of 0.30 mm/wk showed that to be able to demonstrate with 90% power that the lower end of the one-sided 97.5% confidence interval for the difference in lower leg growth rate between two active treatments of inhaled glucocorticoids would be above -0.20 mm/wk (50% of the estimated placebo growth rate of 0.40 mm/wk), 21 subjects had to complete the study (17, 18). The number should be increased by 15–30% to allow for withdrawals.

Short-term knemometry and systemic activity

Using observations periods of 1–4 wk, short-term knemometry is extremely sensitive for assessment of the systemic activity of inhaled glucocorticoids. The method has been proven to define the lowest dose at which systemic activity can be detected, to detect dose-related effects, to compare effects of specific drugs and inhaler devices and to evaluate dose administration regimens (3, 7, 12–20). No other, be it non-invasive or invasive, measure of systemic activity has generated so much information on inhaled glucocorticoids in children. A quite widely used measure such as 12- or 24-h urine free cortisol excretion is less sensitive than short-term knemometry as proven by rigorous comparisons (29, 30) and as confirmed in a number of other trials (10, 17, 18, 31). Whether the invasive extended period measures of cortisol secretion such as 24-h repeated plasma or serum cortisol levels may perform as well or even better than the non-invasive measure of lower leg growth, probably, will not be solved. Such invasive extended measures are difficult to work with in clinical pediatric trials consisting of placebo and several active periods and give rise to ethical concern.

Short-term knemometry implications for intermediate-term height

On the basis of observations in healthy children and in children with growth disorders (23, 24), during many years, it was a dogma that suppressed short-term lower leg growth rates, obtained during less than 3 months in children treated with exogenous glucocorticoids could not be extrapolated to a risk of intermediate-term height growth suppression be it in individuals or in populations of children with asthma. It was supported by the follow up evaluations of intermediate-term height growth and clinical experience, which were not in agreement with the reports of dose-related short-term growth

suppressive effects of inhaled glucocorticoids. The inconsistencies were mostly taken to represent confounding from spontaneous variations in growth rate, short-term soft tissue effects of exogenous glucocorticoids, which may invalidate the short-term measurements, transitory growth suppressive effects of glucocorticoids and reduced adherence to glucocorticoids over time, or to a combination of the factors. As the first knemometry studies of short-term growth effects of inhaled glucocorticoids in children with asthma were published, it was clear that individual short-term growth rates cannot be used for quantifying intermediate-term height growth outcome. For one reason this is simply not possible because of the periodicity in short-term growth. When individual growth curves are analyzed in cross over studies, it is obvious that the sensitivity to short-term growth suppression may change with the rhythmicity. Individual children may present with unaffected growth rates, during treatment with an exogenous glucocorticoid, whereas they may show marked suppression during comparative or placebo periods. Such variations eliminate any possibility of using short-term knemometry for prediction of intermediate-term growth in individuals on inhaled glucocorticoids. This, however, may not rule out that short-term knemometry in populations of children may be capable of identifying inhaled glucocorticoid regimens that may be at risk of suppressing intermediate-term height growth.

When interpreting population based growth results from the available randomized, double-blind knemometry trials of exogenous glucocorticoids, in children with asthma, it is evident that very small reductions in mean growth rates may be seen, be they statistically significant or not (4, 7, 20, 31). As evidenced by recent reports of evaluations of inhaled ciclesonide 160 μg , which was found to cause a non-statistically significant short-term lower leg growth rate suppression of approximately 10%, which was consistent with unaffected 1-yr height growth, such minute reductions have no implications for intermediate-term growth (31, 32). At the other end of the spectrum, however, several studies have provided evidence that the more severe the short-term growth suppression the more likely it is that the glucocorticoid will also cause intermediate-term height growth suppression. Prednisolone 2.5 and 5 mg and inhaled beclomethasone dipropionate 400 μg caused short-term growth rate reductions in the range of 85–95%, which corresponded with 1–2 cm reductions in annual growth rates (3, 7, 17, 19, 33, 34). Thus, intermediate-term

height growth suppressive effects are not nearly as marked as short-term effects. Furthermore, to define more precisely at which level of short-term growth suppression intermediate-term adverse effects may be anticipated, we recently reviewed the published series of randomized, double-blind knemometry studies and compared the results with data from the available randomized, double-blind 1-yr height growth trials of inhaled glucocorticoids (Fig. 2, Table 1) (35). The variations in the short-term growth suppressive potencies of specific glucocorticoids, application systems and doses are clearly seen (Fig. 2). Only the data in the two fluticasone propionate studies were inconsistent. In one of them, 200 μg was associated with a short-term growth rate that was approximately 45% lower than during placebo (7), whereas in the other, it was almost identical with placebo (9). In the first study, placebo growth rates were considerably higher than the mean growth rates of around 0.40–0.50 mm/wk, which have been quite consistently reported in other studies. To some extent this may explain the marked percentage reduction. Even when this is considered, however, the observation in the other study seems incomprehensible. When the data are compared with 1 yr height growth studies in schoolchildren, which have found a reduction of approximately 0.5 cm/yr caused by fluticasone propionate 100 and 200 μg (Table 1) and with double-blind data in pre-schoolchildren in whom fluticasone propionate 88 μg twice daily was associated with a reduction in height growth of 1.1 cm after 2 yr (42) it seems fair to say that short-term lower leg growth and intermediate-term height growth, indeed, may be affected by 200 $\mu\text{g/day}$.

Whether dry powder fluticasone propionate 400 μg , which was associated with a short-term reduction of around 30%, may be at risk of causing intermediate-term growth suppression may be elucidated from the budesonide data. Inhaled dry powder budesonide 200 and 400 μg per day have caused short-term reductions of 25 and 45% and statistically significant 1 yr height growth reductions of 0.5–1.5 cm/yr. There are no rigorous comparative data to interpret the implication of short-term suppression of around 30% of drypowder fluticasone propionate 400 μg , beclomethasone dipropionate 200 and 400 μg from pressurized metered dose inhalers or the report in the present issue of the journal of a suppression by ciclesonide from a metered dose inhaler with a spacer (10). Based on the data from the intermediate-term trials with budesonide however, a short-term suppression of 30% may not rule out a risk of height growth

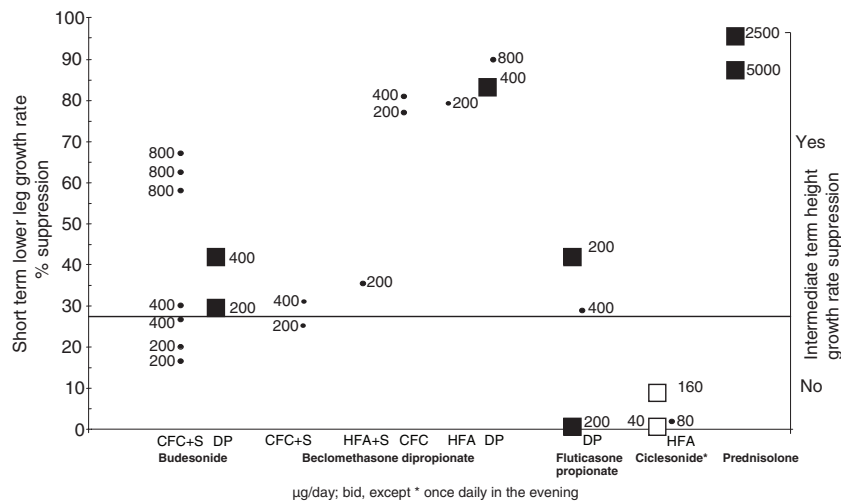


Fig. 2. Results of 13 randomized, double-blind short-term knemometry studies of inhaled glucocorticoids and of oral prednisolene expressed as percentages of placebo lower leg growth rate (LLGR) (3, 4, 7, 9, 12–18, 20, 31). The right hand y-axis is generated from the 1-yr randomized, double-blind height growth rate trials listed in Table 1. ●: % LLGR suppression; ■: % LLGR suppression; 1-yr growth rate assessment(s) found statistically significant suppression □: % LLGR suppression; 1-yr growth rate assessment(s) found no statistically significant suppression. See text for further interpretation. CFC + S, chlorofluorocarbon pressurized metered dose inhaler with a spacer; CFC, chlorofluorocarbon pressurized metered dose inhaler without a spacer; HFA + S, hydrofluoroalkane-134a pressurized metered dose inhaler with a spacer; HFA, hydrofluoroalkane-134a pressurized metered dose inhaler without a spacer; DP, dry powder inhaler.

Table 1. Annual growth rate results in nine randomized, double-blind clinical trials in schoolchildren with asthma treated with inhaled glucocorticoids (IGS) (26–42)

Glucocorticoid daily dose	Comparator	Difference in growth rate with IGS vs. comparator (cm/yr)	Significant difference
Beclomethasone 400 µg	Placebo	−1.1	Yes (p = 0.018)
Beclomethasone 400 µg	Salmeterol	−1.4	Yes (p = 0.004)
Beclomethasone 400 µg	Placebo	−0.78	Yes (p < 0.01)
Fluticasone 200 µg	Placebo	−0.4	No (p = 0.313)
Fluticasone 100 µg	Cromoglycate	−0.5	No (p = 0.11)
Fluticasone 200 µg	Montelukast	−0.41	Yes (p = 0.018)
Budesonide 100 & 200 µg*	Placebo	−1.09; −1.49	Yes (p < 0.01)
Budesonide 200 µg*	Placebo	−0.58	Yes (p < 0.0001)
Budesonide 400 µg	Placebo	−1.1	Yes (p < 0.005)
Ciclesonide 40 & 160 µg†	Placebo	0.02; −0.15	No (95%CI >0.5 m/yr)

*Once daily, †Once daily in the morning.

suppression. From the data in the 1 yr height growth trials of inhaled drypowder budesonide and beclomethasone 400 µg, it is evident that these regimens cause 1 yr height growth rate to be reduced by around 1–1.5 cm/yr. From the observed short-term growth reductions by these treatments of 42 and 85%, respectively, it may be deduced that short-term growth reductions of more than 40% imply intermediate-term height growth suppression. In accord with this, the observed short-term growth suppression, with inhaled budesonide 800 µg, from a metered dose inhaler from a spacer, with beclomethasone dipropionate 200 and 400 µg, from a chlorofluorocarbon or a hydrofluoroalkane-134a pressurized metered dose inhaler without a spacer would be considered to be associated with a significant risk of intermediate-term height growth

suppression. The same applies to the observation reported in the present issue of the journal of a 0.08 mm/wk growth rate during treatment with fluticasone propionate 375 µg/day from a spacer, which correlated with an 81% suppression of placebo growth rate (10).

So, although no specific cut-off level can be identified in individuals from the available randomized, double-blind short-term knemometry and intermediate-term height growth rate studies, good evidence have been provided that if the short-term lower leg growth suppression in populations of children is higher than approximately 25% the risk of intermediate-term growth suppression becomes significant with a mean height growth rate retardation in the range of approximately 0.5–1.5 cm during the first year of treatment (35). The results of the 1-yr

randomized, parallel group trial of inhaled budesonide 200 µg from the Pulaimax® dry powder inhaler reported in the present issue of the journal are very consistent with the analysis (43). The mean 2-wk lower leg growth rate was 0.17 mm/wk in the budesonide group compared with 0.39 mm/wk in the montelukast group, thus representing a 44% suppression. This corresponded with a suppression of mean 1-yr height growth rate in the budesonide group of 1 cm compared to the montelukast group. Furthermore, the analysis was in accord with the results of an open-label, non-randomized 1-yr study of budesonide dry powder 400µg/day from the Turbohaler®, which also indicated that short-term knemometry in population of children is able to predict 1-yr height growth suppression (44).

Conclusions

When validated recommendations for standardization and measurement procedures are used, short-term assessment of lower leg growth by knemometry is a highly accurate and reproducible method for assessment of systemic activity of inhaled glucocorticoids in children. The sensitivity of short-term knemometry is much higher than conventional height growth measurement and makes non-invasive assessment of important factors, such as dose-related effects, administration regimens, devices and specific drugs possible. Helpful information about intermediate-term growth effects of inhaled glucocorticoids can be derived from short-term knemometry in populations. Although rigorous assessments have not yet been provided, the available data suggest that the method is sufficiently sensitive for defining specific glucocorticoids, application devices and doses that do not have an adverse effect on long-term height growth. If knemometry results show suppression of less than approximately 25%, it seems highly unlikely that the drug would be at any risk of affecting intermediate-term height growth. If the short-term suppression is higher than approximately 25%, 1-yr height growth suppression becomes a significant risk. After the first year of continuous daily treatment, especially in 'real life situations', the suppressive effect may be less severe, possibly, due to decreasing adherence rates and development of tolerance. As knemometry is able to discriminate inhaled glucocorticoids with from those without a potential for long-term height growth suppression, short-term knemometry may be recommended as an integral part of the safety

evaluations of new inhaled glucocorticoids and inhalation devices in children with asthma.

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