

Establishing a therapeutic index for the inhaled corticosteroids: Part II

Comparisons of systemic activity and safety among different inhaled corticosteroids

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The systemic activity and safety of inhaled corticosteroids are best studied in randomized, controlled, long-term trials with clinically relevant doses in subjects. These studies require large numbers of enrolled subjects and are difficult to conduct. Potential confounders to safety analyses must be controlled. The occurrence and magnitude of adrenal suppression has been the most extensively evaluated systemic effect of inhaled corticosteroids. The significance of these findings in relation to relevant clinical outcomes must be evaluated. At low to medium inhaled corticosteroid dosages, the hypothalamic-pituitary-adrenal axis is minimally and only partially suppressed. Statistically significant changes occur at high inhaled corticosteroid dosages; the magnitude of this effect is less than with prednisone, ≥ 10 mg/day. Standards for the design of growth studies in children with asthma have been recommended and recently implemented. Four randomized, controlled, clinical trials have reported reductions in growth rates of ≥ 1 cm/yr with beclomethasone ≤ 400 μ g/day. By comparison, 2 randomized controlled clinical trials with fluticasone, 50 to 100 μ g twice daily via dry powder inhaler, could not detect differences in height velocity in prepubertal children treated with cromolyn sodium or placebo. Trials with low to medium doses of beclomethasone, fluticasone, and budesonide document little to no effect on bone mineral density and bone metabolism. Population-based and limited randomized controlled trials suggest that low to medium doses of inhaled corticosteroids do not cause cataracts or glaucoma. Patients requiring high-dose inhaled corticosteroids should be monitored for adverse effects, with appropriate lifestyle changes and pharmacologic strategies implemented. (*J Allergy Clin Immunol* 1998;102:S52-S64)

Key words: *Asthma, inhaled glucocorticoids, safety, growth, clinical trials, cataracts, bone effects, pituitary-adrenal function tests*

An evidence-based approach to the analysis of systemic activity and safety of inhaled corticosteroids (ICS) is essential to make appropriate risk-benefit decisions for individual patients with asthma. Given in high enough dosages, all ICS will produce systemic effects. Yet, even

Abbreviations used

BDP:	Beclomethasone dipropionate
BMD:	Bone mineral density
BUD:	Budesonide
CI:	Confidence interval
CS:	Cromolyn sodium
FP:	Fluticasone propionate
GC:	Glucocorticoid
GH:	Growth hormone
HPA:	Hypothalamic-pituitary-adrenal (axis)
ICS:	Inhaled corticosteroid(s)
MDI:	Metered-dose inhaler
OR:	Odds ratio
PSC:	Posterior subcapsular cataract
RCT:	Randomized controlled trial
TA:	Triamcinolone acetonide

high dosages of ICS are preferable to oral corticosteroid therapy in the patient with severe persistent asthma. Therefore safety analyses must be performed with severity-appropriate ICS regimens in the targeted population.

Long-term effects of ICS are difficult to assess because of the confounding influence of many factors including the use of oral corticosteroids for rescue therapy and the effects of chronic asthma itself. Several studies to date have been performed in healthy volunteers, yet it is unknown whether these results can be generalized to patients with mild to moderate asthma, let alone to those with severe disease. As in efficacy trials, studies of drug delivery systems must be comparative and must account for differences in inhalation technique and regimen adherence among subjects.

This article focuses on the effects of ICS on growth, bone, eye, and the hypothalamic-pituitary-adrenal (HPA) axis, reviewing only adequately controlled studies in asthmatic populations. The complexities of the studies are identified, and standards for analysis are also recommended.

GROWTH

Mechanisms of growth suppression by glucocorticoids

Growth effects of ICS are of increasing interest to

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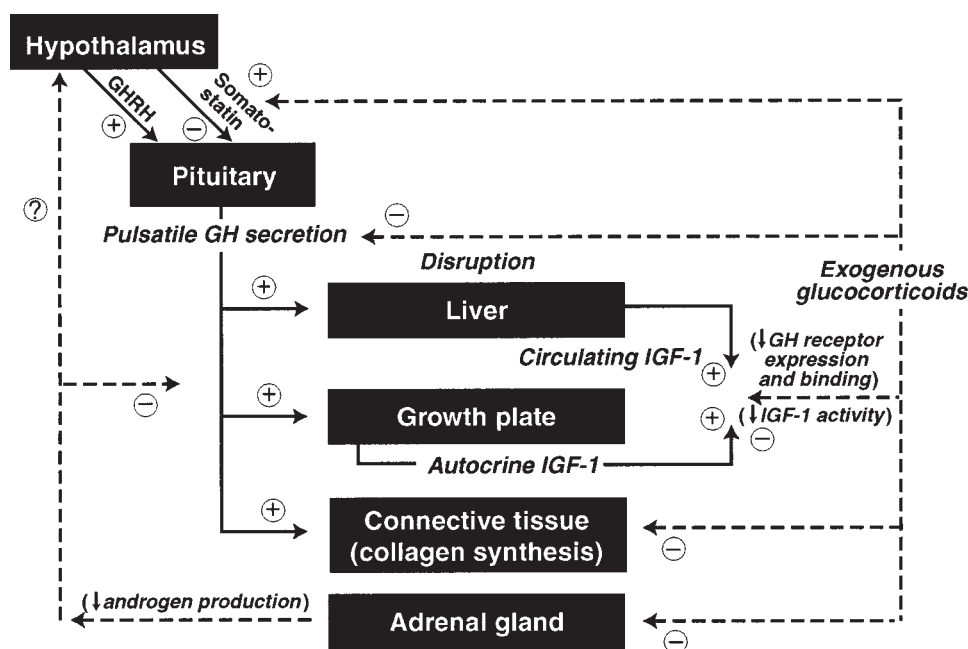


FIG 1 Mechanisms of linear growth inhibition by GCs. Growth-suppressing influences of exogenous GCs on pulsatile GH secretion, IGF-1 bioactivity, GH-receptor expression, collagen synthesis, and adrenal androgen production (proposed) are depicted. GH, Growth hormone (pituitary), IGF-1, insulin-like growth factor-1; GHRH, growth hormone releasing hormone (pituitary). Reproduced with permission from Allen DB. The influence of inhaled corticosteroids on growth: a pediatric endocrinologist's perspective. *Acta Paediatr* 1997;86:1-7.

clinicians, because current clinical management guidelines^{1,2} continue to recommend early intervention with ICS in appropriate patients,^{3,4} and the prospect of life-long ICS therapy in those patients presents specific long-term concerns. The pathogenesis of growth suppression by glucocorticoids (GCs) involves several steps in the cascade of events leading to linear growth.⁵ Fig 1 schematically represents these inhibitory mechanisms. Glucocorticoids are potent inhibitors of virtually every component of the growth axis including growth hormone (GH) secretion and action, insulin-like growth factor-1 bioactivity, collagen synthesis, and adrenal androgen production. The most important effect responsible for growth failure is still uncertain. The complexity of interactions between GC and growth makes it likely that a compounding of effects will determine the extent of growth impairment in an individual.⁵

Growth in asthma

Childhood growth occurs in 3 phases.⁶ During the first 2 years of life, growth is rapid but decelerating and is determined mainly by nutrition. In the second phase childhood growth is relatively steady until the onset of puberty and is regulated by the GH axis. Finally, the pubertal growth spurt occurs, controlled by both GHs and sex steroids.

Growth occurs in discontinuous bursts interrupted by long, growth-free periods. Half of normal prepubertal

TABLE I. Standards for designing studies of growth

Baseline comparisons between treatment and control groups
Asthma severity
Age
Pubertal status
Bone age
Heights and growth rates
Auxology issues
Baseline observation of growth rate for 6 mo
Sample size determination to detect decline in growth rate of 1 cm/yr
Stadiometer measurements of height
Limited number of trained observers
Consistency in time of day of measurements
3- to 4-mo interval between measurements
Careful sexual maturation staging by physical examination
Minimum study duration of 12 mo
Growth data analysis
Determination of annual growth velocity by fitting a regression line
Clear segregation of pubertal and prepubertal patients
Calculation of height and growth velocity standard deviation scores for age and bone age
Comparison of observed heights and growth velocity with expected values for age
Comparison of individual growth velocity with baseline growth rate

Modified with permission from Allen DB. The influence of inhaled corticosteroids on growth: a pediatric endocrinologist's perspective. *Acta Paediatr* 1997;86:1-7.

TABLE II. Summary of growth studies with BDP

Study	Study population	Trial design/Regimen	Safety outcomes	Comments
Tinkelman 1993 ²³	195 children aged 6-16 yr (mean, 11.9 ± 2.7); mild-moderate asthma (mean FEV ₁ , 74%)	Multicenter, double-blind, randomized, double placebo-controlled trial of BDP MDI 84 µg four times daily or theophylline SR twice daily (target concentration 8-15 µg/mL) for 12 mo	Growth velocity 4.4 cm/yr for BDP and 6.0 cm/yr for theophylline (<i>P</i> = .001); no evidence of PSC or glaucoma	Growth velocity suppression greater in boys; no alterations in cortisol measurements either at baseline or after stimulation
Doull 1995 ²⁴	94 prepubertal children aged 7-9 yr; mild asthma (mean FEV ₁ , 88%)	Multicenter, double-blind, randomized, placebo-controlled, community-based trial of BDP 200 µg twice daily or placebo via Diskhaler for 7 mo, followed by washout period for 4 mo (mean compliance, ~75%)	At 7 mo, BDP-treated children had grown significantly less than placebo children (mean, 2.66 vs 3.66 cm, respectively; <i>P</i> < .0001)	Growth significantly decreased in both males and females; during 4-mo washout period, no significant catch-up growth; BDP had no effect on overnight urinary cortisol production
Simons 1997 ²⁵	Children aged 6-14 yr; mild asthma (FEV ₁ >70% predicted, 10% reversibility and PC ₂₀ methacholine <8 mg/mL)	Multicenter, randomized, double-blind, placebo-controlled, parallel-group 1-yr study of BDP 200 µg twice daily, salmeterol 50 µg twice daily, placebo twice daily via Diskhaler	During mo 1-12, linear growth 3.96 cm in BDP group, 5.40 cm in placebo group (<i>P</i> = .018)	
Verberne 1997 ²⁶	Children aged 6-16 yr; mild to moderate asthma (FEV ₁ , 55%-90% predicted, 10% reversibility and PD ₂₀ methacholine ≤150 µg)	Multicenter, randomized, double-blind, parallel-group, 1-yr trial of salmeterol 50 µg twice daily or BDP 200 µg twice daily via Diskhaler	Growth significantly slower in BDP group (-0.28 SDS) vs salmeterol group (-0.03 SDS) (<i>P</i> = .001); mean ↑ height 6.1 cm in salmeterol group vs 4.7 cm in BDP group (<i>P</i> = .007)	Study stratified for sex, age, study center, baseline FEV ₁ , baseline PD ₂₀ , previous ICS use

BDP, Beclomethasone dipropionate; FEV₁, forced expiratory volume (in one second); MDI, metered-dose inhaler; SR, sustained-release; SDS, standard deviation scores; PSC, posterior subcapsular cataracts; PC₂₀, provocative concentration [of methacholine] causing a 20% fall in FEV₁.

children show seasonal variation in lower leg growth and in height velocity. These growth patterns likely contribute to the lack of correlation between short- and long-term growth.⁷

A physiologic, decelerating growth-velocity pattern, often associated with delay in the onset of puberty, has been reported for children with asthma, independent of disease severity or treatment.⁸ Most children with asthma, however, attain a normal final adult height, with the possible exception of those with severe persistent disease.^{9,10} It is likely that the frequency of symptoms and the degree of asthma control have important effects on the growth rate¹¹ and are therefore potential confounders of ICS growth studies.

Growth measurement

Knemometry, a sensitive technique of measuring growth of the lower leg, has been used to compare systemic effects of different ICS in children, demonstrating ICS dose-response relations.^{12,13} Although the results of knemometry are accurate and reproducible, the clinical

implication of these findings is unclear. Some data suggest that knemometry is too sensitive and may therefore amplify or exaggerate the growth-retarding effects of exogenous steroids.¹⁴ Limitations of short-term knemometry studies include variations in normal growth patterns (eg, seasonal patterns and "spurts"), the need for large and homogeneous samples, and the need to perform measurements at the same time of day in all subjects in the study to account for the potential of leg-shrink phenomenon.¹⁵⁻¹⁷ The relationship of short-term growth changes, as determined by knemometry, to overall height velocity and to the attainment of adult height remains to be determined.^{16,18,19}

Most pediatric growth experts conclude that standing height and height velocity are best measured by a quality stadiometer that is properly serviced and calibrated and is operated by trained personnel.^{5,6} For a 1-year growth assessment, height should be averaged from 3 separate recordings measured at approximately 3-month intervals. Growth rate can then be computed by fitting a regression line to the points, with the slope reflecting

TABLE III. Summary of growth studies with BUD

Study	Study population	Trial design/Regimen	Safety outcomes	Comments
Merkus 1993 ²⁷	40 teenagers (mean age, 12.8 yr) with asthma (FEV ₁ , 55%-90% predicted) vs 80 control subjects matched for sex, age, and height	Subjects with asthma randomized to BUD MDI 200 µg three times daily vs placebo for median follow-up of 22 mo	Growth rates in male asthmatics, but not in female asthmatics, significantly less than in control children ($P < .05$); mean difference in growth rates between BUD-treated asthmatics and controls, -0.44 cm/yr; between placebo-treated asthmatics and controls, -0.70 cm/yr (NS)	Estimated compliance with BUD, 74%
Agertoft 1994 ²⁸	216 children aged 3-6 yr (at baseline) evaluated at 6-mo intervals for 1-2 yr without BUD, then 3-6 yr with BUD vs 62 control children evaluated for 3-7 yr; mean FEV ₁ , ~80%	Controlled prospective study of BUD 800 µg/day for 6-8 wk, with continual attempts to treat the child with minimal-effective BUD dose vs controls (children whose parents did not wish ICS treatment)	No statistically significant changes seen in growth velocity or weight gain during BUD	During BUD treatment, mean daily dose ↓ from 710 to 430 µg ($P < .01$) over observation period; both Nebuhalers and Turbuhalers used

BUD, Budesonide; FEV₁, forced expiratory volume (in 1 second); MDI, metered-dose inhaler; NS, not significant; ICS, inhaled corticosteroids.

growth velocity.²⁰ The use of a height velocity standard deviation score is further recommended⁶ and can be calculated as follows: height velocity - mean height velocity/SD. Mean height velocity and the SD are calculated from a pediatric population of the same sex and age as the patient.

Growth study design

Potential confounders that may impede the accurate assessment of ICS growth effects include extent of asthma severity and disease control, influence of atopy, genetic factors, influence of sex and pubertal status, previous oral corticosteroid and ICS use, nutritional factors, and growth measurement techniques. Allen⁵ has recommended standards for the design of growth studies in children with asthma, which are summarized in Table I. Only randomized controlled trials (RCTs) that incorporate the most important of these design parameters have been included in this review.

Growth Studies With ICS

The effect of ICS on long-term (achievement of adult height), intermediate-term (>6 months), and short-term (≤6 months) growth have been previously reviewed by Wolthers.²¹ In addition, a meta-analysis of the effect of ICS on growth was published by Allen et al.²² Data on beclomethasone dipropionate (BDP) predominate because of its long availability in the international marketplace. Based on the meta-analysis, Allen et al²² concluded that moderate-dose BDP (400 to 600 µg/day) was unlikely to have a clinically significant effect on linear growth and could be considered safe treatment. According to these authors, higher doses (>800 µg/day) might be expected to result in more frequent and profound growth suppression, but further studies were required to make this conclusion.²²

Since these 2 reviews were published, 4 randomized, double-blind, controlled trials of BDP ≤400 µg/day have been published and are described in Table II.²³⁻²⁶ Tinkelman et al²³ evaluated BDP 84 µg four times daily with a metered-dose inhaler (MDI); the other 3 trials evaluated BDP 200 µg twice daily with the dry powder Diskhaler delivery system.²⁴⁻²⁶ All 4 studies reported a statistically significant reduction in growth velocity in the BDP-treated group; the magnitude of this decline in growth rate ranged from -1.08 cm/yr to -1.7 cm/yr. In the only trial that incorporated a 4-month washout period at the conclusion, no significant "catch-up" growth was observed.²⁴

Two controlled trials (1 randomized) evaluating the growth effects of budesonide (BUD) are described in Table III.^{27,28} Merkus et al²⁷ studied 40 teenagers with asthma and 80 matched subjects in a control group without asthma. They were able to detect changes in growth rates in male asthmatics but not in female asthmatics compared with the children in the control group. No statistically significant growth rate changes were seen with BUD. This trial used BUD 200 µg 3 times daily with MDI, not the U.S.-marketed Turbuhaler. Agertoft and Pedersen²⁸ evaluated 216 prepubescent children with asthma treated with BUD and compared them with 62 children with asthma in a control group (ie, children whose parents did not wish ICS therapy). The BUD group was initially treated with 800 µg/day, with continued attempts to reduce to the minimally effective dose. Both Nebuhaler and Turbuhaler delivery systems were used to administer BUD to these children, complicating the analysis. No statistically significant changes were observed by the investigators in growth velocity during the 3- to 7-year observation period.

Two earlier open-label studies^{29,30} with BUD 100 µg twice daily with Nebuhaler evaluated prepubertal children (aged 2 to 7 years) with asthma. During the 1- to 5-

TABLE IV. Summary of growth studies with FP

Study	Study population	Trial design/Regimen	Safety outcomes	Comments
Price 1997 ³¹	Prepubertal children aged 4-10 yr with mild asthma	Multicenter, open-label, randomized, parallel-group study of FP 50 µg twice daily Diskhaler vs CS 20 mg four times daily Spinhaler for 12 mo; powered to demonstrate equivalence of treatment in effect on height velocity	No significant differences between patients who received FP (n = 34) and CS (n = 26) for 1 yr in terms of height velocity adjusted for age and sex, or height velocity SD scores adjusted for sex; mean velocities reported, 6.0 ± 0.1 cm/yr for FP and 6.5 ± 0.5 cm/yr for CS	No differences in mean 24-hr urinary free cortisol levels at 6 and 12 mo
Allen 1998 ³²	Prepubertal girls aged 4-9 yr and boys aged 4-11 yr with FEV ₁ ≥ 60% predicted (target enrollment = 90 patients per group); normal growth at enrollment	Prospective, randomized, double-blind, parallel-group trial of FP 50 µg or 100 µg or matching placebo, twice daily via Diskhaler; 80% power to detect 1.0 cm/yr difference in height velocity	No statistically significant differences in mean height, mean growth velocity, or mean skeletal age between any of the treatment groups at any time (6.15 ± 0.17 cm placebo, 5.94 ± 0.16 cm FP 50 µg, 5.73 ± 0.13 cm FP 100 µg, <i>P</i> = .308)	Growth analysis based on children who continued prepubescent during the trial; a small drug effect could not be definitively excluded, but slight difference in growth rates may have been confounded by dropout rate in placebo group (23%) vs FP (2%-4%); no significant differences noted in drug-related ADRs, HPA-axis measurements, or eye exams

CS, Cromolyn sodium; FP, fluticasone propionate; ADR, adverse drug reaction; HPA, hypothalamic-pituitary-adrenal (axis).

year observation periods, no growth pattern changes were reported with BUD; all children grew according to their height and weight percentiles. Bone age advanced normally in both studies.

Two RCTs with fluticasone propionate (FP) Diskhaler are described in Table IV.^{31,32} Price et al³¹ compared FP 50 µg twice daily via Diskhaler with cromolyn sodium (CS) 20 µg 4 times daily with Spinhaler in a 12-month, open-label, randomized, parallel-group trial. This study was powered to demonstrate equivalence of treatment effect on growth velocity. Height was measured by stadiometry. No significant differences in height velocity could be detected between treatment groups of prepubertal children (mean velocity, 6.0 ± 0.1 cm/yr for FP and 6.5 ± 0.5 cm/yr for CS).

Allen et al³² evaluated 2 doses of FP with Diskhaler (50 µg or 100 µg twice daily) in a 52-week, prospective, randomized, double-blind, placebo-controlled, parallel-group trial. Prepubertal children with asthma (forced expiratory volume in 1 second >60% predicted) were eligible if they had documented normal growth patterns at entry (height centile, 5th to 95th; growth velocity centile, 10th to 97th) and sexual maturity ratings of 1 (Tanner scale). Enrollment was targeted to 90 patients per treatment group to have 80% power to detect a 1.0 cm/yr difference in height velocity. Children were excluded if they had used significant (>60 days) systemic corticosteroid therapy within the previous 2 years but were allowed to take ICS, theophylline, or CS before enrollment. Eligible patients were stratified by ICS use at study entry. Children

were withdrawn from the study if they required more than two 7-day bursts of oral corticosteroids during the trial.

Height measurements were performed by Harpenden stadiometry (Holtain, Wales) at 4-week intervals; bone age films of the left hand and wrist were obtained at baseline and at weeks 24 and 52. Tanner sexual maturity ratings were performed at 4-week intervals. Growth analyses were based on the entry population minus those who achieved pubescence during the trial. No statistically significant differences in mean height, mean growth velocity, or mean skeletal age among any of the treatment groups were detected at any time (*P* = .308, overall). Nearly all children participating in this study grew at normal rates for this age group irrespective of treatment allocation. The authors stated that a small drug effect could not be definitively excluded; the slight difference in growth rates may have been confounded by the dropout rate in the placebo group (23%) versus the treatment group (2% to 4%).

RCTs of triamcinolone acetonide (TA) or flunisolide are not available. In an early retrospective review of the effects of 1 year of open-label TA treatment on growth patterns of 82 children with asthma, the authors reported no adverse effects on height.³³ These children ranged in age from 6 to 17 years; 59% were dependent on oral corticosteroids at entry. Baseline heights were below the normal population average. During the 1-year course of TA therapy, patients grew in height as expected (compared with predicted National Center for Health Statistics norms). At the end of 1 year of TA treatment, 65% of

children had completely withdrawn from oral corticosteroids, and 25% were taking less than 10-mg prednisone equivalents. Because of the confounding factors in the study design, these TA growth results cannot be generalized to other populations.

There is a paucity of data on the final outcome of growth, adult height, in children treated with ICS. Silverstein et al³⁴ have published a retrospective cohort analysis of residents in Rochester, Minnesota, with onset of asthma from 1964 to 1987. They studied 153 patients with asthma (mean age at onset, 6.1 ± 4.8 years) and 163 age- and sex-matched nonasthmatic subjects. The adult height of patients with asthma (mean age at measurement, 25.7 ± 5.2 years) was not significantly different from the adult height of nonasthmatic subjects; the overall difference, adjusted for mid-parental height, was -0.20 cm (95% confidence interval [CI], -0.27 to 1.64). The adult height of asthmatic children treated with ICS was not significantly different from the adult height of patients with asthma not treated with ICS.

Although these data should reassure the health care community and parents and patients with ICS-managed asthma, the study design has obvious limitations. Glucocorticoid exposure was assessed from medical record review; verification of actual medication exposure or regimen adherence was not possible. This study was not designed to detect potential differences between the available ICS preparations.

Growth studies: Conclusions

Growth studies with ICS, incorporating improved design standards, are becoming available to the asthma community and will allow for more incisive risk/benefit analyses. Recently published RCTs mandate a reconsideration of the potential growth-retarding effects of ICS. Contrary to earlier studies, BDP at doses previously considered safe can significantly reduce growth velocity. How can these new data be reconciled with previous experience?

Lemanske and Allen³⁵ have suggested 1 possible explanation. As with all RCTs, these 4 BDP studies incorporated a consistent dosage regimen emphasizing adherence. Most patients with asthma require titration of their ICS regimens, either physician-initiated, based on disease control, or self-initiated, based on asthma symptoms, side effects, or cost considerations. Therefore a dose of $400 \mu\text{g}$ every day may not reflect "real life" experience.

The age range and pubertal status in these 4 BDP trials must also be considered. The Tinkelman et al,²³ Simons et al,²⁵ and Verberne et al²⁶ studies enrolled children ranging from ages 6 to 16 years, with a study design primarily oriented to efficacy analysis. The authors do not report the exact number of children in prepubertal and pubertal subgroups, nor do they account for the statistical handling of children who have pubertal transition during the study. It is likely that 50% of female patients enrolled in these trials were pubertal, given the mean age at enrollment. Mean growth data alone are presented in these studies, not individual subject or subgroup growth velocities. However, it

is unlikely that outliers drove the data in these 4 BDP studies, given the consistency of the results.

It should also be recognized that these 4 BDP trials were conducted in study populations with mild to moderate asthma, and therefore the results cannot be extrapolated to patients with more severe disease. Differences in lung absorption among patients with varying asthma severity have been reported. All 4 of these studies used chlorofluorocarbon propellant BDP or dry powder Diskhaler. Therefore these growth studies must be replicated with the BDP hydrofluoroalkane delivery systems to perform an accurate risk/benefit analysis for this future ICS preparation.

The possibility of a drug-specific versus an ICS class-specific effect should be considered. BDP may have a greater systemic effect than other ICS agents because of the intrapulmonary metabolism of BDP to beclomethasone monopropionate.³⁶ BDP also exhibits different first-pass metabolism characteristics, as previously described.

The results of recent RCTs may begin to differentiate the effects of specific ICS agents on growth. The cited BUD trials have study design constraints and require additional RCT evidence. However, the FP study designs, primarily oriented to safety analysis, provide strong evidence of minimal growth retardation effects when FP is administered in doses of 50 to $100 \mu\text{g}$ twice daily with Diskhaler.

EFFECTS ON BONE MINERAL DENSITY AND BONE METABOLISM

Mechanisms of ICS bone effects

Corticosteroids influence both bone formation and bone resorption.^{37,38} The enhanced resorption is likely explained both by the development of secondary hyperparathyroidism and a direct effect on bone.³⁷ When given initially, corticosteroids increase secretion of parathyroid hormone, probably because of reduced intestinal absorption and increased renal loss of calcium. There is also evidence that corticosteroids potentiate the activity of parathyroid hormone on osteoblasts. In addition, corticosteroids inhibit calcium absorption.

Corticosteroids affect the secretion of sex hormones, in turn increasing bone resorption. There is a direct effect on gonadal function by inhibition of pituitary gonadotropin secretion and a direct effect on the testes and ovaries. Corticosteroids inhibit secretion of various hormones including estrogen and testosterone, contributing to further bone loss.³⁹

The main bone effects of corticosteroids are a diminished amount of new bone formed. This reduced bone formation is attributed to a direct effect on osteoblast function and has been well documented by both biochemical and histomorphometric studies.^{37,40,41}

Evaluation of corticosteroid effects on bone

The bone effects of corticosteroids can be evaluated by measurement of biochemical markers of metabolism (both formation and degradation), bone mineral density

(BMD), or frequency of fractures. Long-term fracture rate is the most clinically relevant end point by which to assess ICS effects on bone, but fracture study data are limited.

Metabolic markers of bone metabolism

There has been much interest in the use of metabolic bone markers as surrogates for change in resorption and formation.⁴² Key markers of bone resorption include hydroxyproline, pyridinium cross-links (ie, pyridinoline and deoxypyridinoline), and calcium, as measured in the urine. Bone formation markers are measured in the serum and include osteocalcin (bone gla protein), bone-specific alkaline phosphatase, and procollagen peptides (procollagen type 1 carboxy terminal propeptide and procollagen type 1 N-terminal propeptide). Although these markers have a role in signaling short-term changes in metabolism if sequentially measured, there is great interindividual variation. Furthermore bone turnover markers have varying degrees of sensitivity and specificity that differ among different assays. No single marker has been validated as a reliable and predictable guide to the extent of bone formation or resorption; the significance of some markers is also unclear.^{43,44} The clinical implications of short-term changes in these markers are unknown, because long-term studies suggest compensatory mechanisms may come into operation.⁴⁵

Bone density

Bone density measurements provide direct measures of skeletal health, and they have been shown to correlate with fracture risk.⁴² The most commonly used and best-validated technique for BMD measurement of cortical and trabecular bone in central sites is dual-energy x-ray absorptiometry. Trabecular bone of the lumbar spine can also be assessed by quantitative computed tomography scanning. Quantitative computed tomography scanning may be more sensitive to BMD changes over time because of a greater turnover rate of trabecular bone versus cortical bone. Dual-energy x-ray absorptiometry has been used in both population screening and individual fracture risk assessment. BMD likely predicts fracture with approximately the same power that blood pressure predicts stroke. More specifically, a decrease in BMD of 1 SD below the population norm is associated with a 1.4- to 3.5-fold increase in fracture risk.⁴⁶

Bone effects

Study design. A variety of patient-specific and lifestyle factors are potential confounders to the accurate assessment of long-term ICS effects on bone. These factors include sex, age, menopausal status, gonadal status, smoking history, alcohol intake, calcium intake, exercise status, concurrent drug use (eg, corticosteroid rescue therapy, thiazide diuretics, anticonvulsants, estrogens), and concurrent diseases.⁴⁷ Severe asthma itself may affect BMD because of patient lifestyle changes such as decreased exercise tolerance and possible dietary restrictions. Long-term BMD studies with ICS must either control for or eliminate these confounding factors.

Bone studies with ICS. Toogood et al⁴⁸ reviewed 9 published surveys of BMD in patients who had received ICS therapy. The reported BMD results were conflicting. Those studies that detected a reduction in BMD were confounded by the effects of past or current oral corticosteroid therapy and by postmenopausal patient status.

More recent trials in both children and adults, which have incorporated better study methods and the use of BMD as a primary outcome measure of ICS bone effects, are described in Table V.⁴⁹⁻⁵⁹ Martinati et al⁴⁹ evaluated 64 prepubertal children with mild to moderate asthma treated with either BDP 150 to 600 µg/day or CS 30 mg/day. At the end of 6.7 ± 1.3 months of therapy, bone mineral areal density and volume bone density did not differ in the 2 groups. Furthermore anteroposterior bone density in this study population was in agreement with published normative data and with that of normal, age-related, healthy, nonasthmatic children living in the same area who had the same dietary calcium intake.

In another cross-sectional study involving children, Agertoft and Pedersen⁵⁰ reported on their 3- to 6-year observations with BUD treatment compared with an asthma control group. No statistically significant differences were found between the 2 groups in BMD, bone mineral capacity, total bone calcium, or body composition. Furthermore no correlations were found between any of these parameters and duration of treatment, accumulated dose of BUD, or current dose of BUD.

Two cross-sectional long-term studies in adults with asthma treated with ICS compared with control groups have recently been reported.^{51,52} Wisniewski et al⁵¹ found no significant difference in mean BMD values between those who were and those who were not taking ICS in men or women. However, cumulative ICS was associated with a reduction in posterior-anterior and lateral lumbar spine BMD in women. Luengo et al⁵² concluded that BMD was reduced at 2 years in both ICS-treated asthmatics and patients in a control group. No correlation was found between BMD values and ICS doses or the duration of ICS treatment.

Results of comparative trials with different ICS preparations have also recently become available. To evaluate the effects of FP and BDP in clinically equipotent dosages on indexes of bone metabolism, Bootsma et al⁵³ designed a randomized, double-blind, crossover study consisting of two 6-week treatment periods, each preceded by a 3-week, single-blind, placebo period. BDP significantly reduced 2 indexes of bone formation; FP did not change any variable. Neither treatment increased markers of bone resorption. However, BMD measurements were not performed in this trial.⁵³

In a prospective, open, randomized, parallel-group study of FP 500 µg twice daily versus BUD 800 µg twice daily with MDI and large spacer, Hughes et al⁵⁴ reported normal spinal BMD in both treatment groups after 1 year of treatment ($P = .36$). Serum osteocalcin increased significantly from baseline in both groups with no change in other bone markers. Pauwels et al⁵⁵ described a randomized, double-blind, crossover trial of BDP 500 µg twice

TABLE V. Bone effects of ICS

Study	Study population	Trial design/Regimen	Bone outcomes	Comments
Martinati 1996 ⁴⁹	64 prepubertal children aged 5-10 yr (mean, 6.7 ± 1.2) with mild to moderate asthma	Cross-sectional study of BDP 150-600 µg/day and CS 30 mg/day (control group) for 6.7 ± 1.3 mo	BDP treatment at study dosages not associated with reduced trabecular and cortical bone mass; cortical and trabecular bone density did not differ between children receiving BDP or CS and children treated with higher doses of BDP	Males and females were not different for height, weight, and body mass index in each group and between treated and control groups
Bootsma 1996 ⁵³	21 nonsmoking subjects aged 18-55 yr (mean, 30.3 yr) with asthma (FEV ₁ ≥50% at end of 3-wk, placebo controlled, run-in period); all subjects were regularly receiving BDP or BUD at entry (mean duration, 5.4 yr)	Randomized, double-blind, placebo-controlled, crossover study of FP 375 µg, or BDP 750 µg, or placebo by MDI twice daily for two 6-wk treatment periods	BDP ↓ both osteocalcin and procollagen type 1 carboxy terminal propeptide, indexes of bone formation, significantly by 18.5% and 21.9%, respectively; FP did not change any variable of bone formation; FP and BDP did not change any variable of bone formation; FP and BDP did not ↑ type 1 collagen carboxy terminal telopeptide and deoxypyridinoline cross-links, both markers of bone resorption	Neither treatment changed morning cortisol
Hughes 1996 ⁵⁴	59 patients previously treated with BDP 1500-2000 µg/day or BUD 1200-1600 µg/day; patients excluded if they received significant oral corticosteroids previously	Prospective, open, randomized, parallel-group study of FP 500 µg twice daily vs BUD 800 µg twice daily by MDI and large spacer for 1 yr	Spinal BMD was normal at baseline and increased in both groups after 1 yr (0.5% FP, 1.6% BUD; <i>P</i> = .36); serum osteocalcin increased significantly from baseline in both groups (16.9% FP, 14.3% BUD)	
Wisniewski 1997 ⁵¹	81 subjects aged 20-40 yr with asthma (men: mean FEV ₁ , 3.87 without ICS and 3.40 with ICS; women: mean FEV ₁ , 3.13 without ICS and 2.83 with ICS)	Cross-sectional study of subjects who had never taken ICS or systemic steroids compared with subjects who had taken ICS ≥5 yr with limited exposure to systemic steroids in the past (self-administered questionnaire, spirometric tests, BMD measurements, lateral thoracic and lumbar radiography)	No significant difference in mean BMD values in men or women between those who were and those who were not on ICS; cumulative ICS dose, however, was associated with a reduction in posterior-anterior and lateral lumbar spine BMD in women (0.11 SD reduction in lumbar spine BMD for every yr use of 1000 µg/day ICS, after correction for confounding factors)	ICS therapy reduced BMD in the spine in women, but was not associated with other markers of bone metabolism in women (at the hip or wrist) or men (at any skeletal site) or with the presence of vertebral fractures
Luengo 1997 ⁵²	48 asthmatic adults (mean age, 56 yrs) (% FEV ₁ , 70 ± 18 predicted); 48 nonasthmatic adults (mean age, 55 yr)	Cross-sectional study of asthmatic patients taking a mean daily dose of 662 ± 278 µg of ICS for >1 yr (mean duration of treatment, 10.6 yr) followed for a 2-yr period with a spacer attached to the subject's inhaler compared to subjects who had never taken ICS	BMD ↓ both in asthmatics (<i>P</i> = .002) and controls (<i>P</i> = .008) at 2 yr; no significant differences in BMD loss between patients and healthy subjects; both female asthmatics (<i>P</i> = .002) and female controls (<i>P</i> = .013) showed a significant loss of bone mass	No correlation was found between ICS doses or the duration of treatment and BMD values; no differences in the rate of bone loss were found between patients who had received booster courses of oral corticosteroids and those not treated with this therapy
Ford 1997 ⁵⁷	64 subjects (males 18-50 yr; females 18-40 yr and premenopausal) with mild asthma, FEV ₁ ≥60%; normal baseline spine BMD and HPA axis at entry	Multicenter, double-blind, randomized, placebo controlled trial of FP 500 µg twice daily vs placebo Diskhaler for 2 yr	No statistically significant differences in treatment groups in BMD compared with baseline (<i>P</i> = .801); 2 patients in each treatment group had a bone loss rate-of-change >5% during the course of the study	One subject on FP 500 µg twice daily had an abnormal ACTH stimulation test during the course of the trial; no PSC or evidence of glaucoma in either treatment group

TABLE V. (CONT'D) Bone effects of ICS

Study	Study population	Trial design/Regimen	Bone outcomes	Comments
Agertoft 1998 ⁵⁰	157 BUD-treated children aged 5-16 yr (mean FEV ₁ , 97%); 111 control group children aged 5-16 yr (mean FEV ₁ , 81%)	Cross-sectional study of children with asthma treated for ≥3 yr with BUD (total accumulated dose: mean, 813.1 mg; range, 249-2800 mg) compared with children with asthma who had never received ICS (all children evaluated q 6 mo for 3-6 yr)	No statistically significant differences between the 2 groups in BMD, BMC, TBC, or body composition; no correlation between bone measurements and duration of treatment, accumulated or current dose of BUD	Males and females were not different for height, weight, or age between treated and control groups at entry; continued attempts during observation period to treat with minimal effective dose of BUD; estimated BUD compliance, 78% (range, 42%-110%)
Pauwels 1998 ⁵⁵	306 subjects aged 18-75 yr (mean age, 46.6 yr in group that started with FP and finished with BDP; mean age, 46.2 yr in group that started with BDP and finished with FP) with moderate to severe asthma; all subjects were on regular treatment with BDP or BUD 800-2000 µg/day	Multicenter, randomized, double-blind, crossover study of salmeterol 50 µg twice daily for 1 mo, then BDP 500 µg or FP 250 µg twice daily for 11 mo	Osteocalcin and BMD were improved over baseline in the FP group, resulting in higher serum osteocalcin levels and higher BMD in the spine ($P = .05$), femoral neck ($P < .01$), and Ward's triangle ($P = .01$) compared with BDP	No significant differences between the 2 treatments regarding morning plasma cortisol or urinary excretion of calcium and hydroxyproline at any time point during the study
Medici 1998 ⁵⁶	69 recruited subjects with asthma (mean age, 39 yr; 67% male); all females premenopausal	Multicenter, randomized, parallel-group study comparing the effects of FP 400 µg/day vs BDP 800 µg/day and FP 750 µg/day vs BDP 1500 µg/day on BMD and bone metabolism over 1 yr of treatment	DEXA of lumbar spine in the low-dose group ($P = .022$) in favor of FP 400 µg/day; compact bone BMD of the proximal radius in the high-dose group ($P = .048$) in favor of BDP 1500 µg/day	Little or no evidence of any important differences between equipotent FP and BDP in their effects on BMD or bone metabolism
Osuri 1998 ⁵⁸	144 adults with asthma	Prospective, blinded, placebo-controlled analysis of FP 88 and 440 µg twice daily MDI for 6 mo	Normal response defined as lumbar spine bone loss rate-of-change < 5%; no significant changes observed in the 3 treatment groups	No subject demonstrated signs of glaucoma or PSC
Tattersfield 1998 ⁵⁹	374 subjects (205 female; 18-66 yr; FEV ₁ , 86% of predicted)	Randomized, 2-yr, prospective, open, parallel-group study to document changes in BMD in subjects with mild asthma; patients randomized either to BUD 400 µg/day MDI, BDP 500 µg/day MDI, or Ref	There was no statistically significant difference in BMD changes after 24 mos of treatment; only 4 fractures occurred, distributed evenly between groups	Treatment-failures or asthma-deteriorations were few (BUD, 0; BDP, 1; Ref, 8); number of short courses of oral steroid during study: BUD, 38; BDP, 34; Ref, 96

FP, Fluticasone propionate; BDP, beclomethasone dipropionate; CS, cromolyn sodium; BMD, bone mineral density; SD, standard deviation; BUD, budesonide; BMC, bone mineral capacity; TBC, total bone calcium; ICS, inhaled corticosteroid(s); HPA, hypothalamic-pituitary-axis; PSC, posterior subcapsular cataract; DEXA, dual energy X-ray absorptiometry; Ref, nonsteroid reference therapy.

daily versus FP 250 µg twice daily for 11 months in an adult group of asthmatics previously treated with BDP or BUD 800 to 2000 µg/daily. Even though these ICS doses were equally efficacious, FP was associated with higher BMD (as assessed at the hip) and higher serum osteocal-

cin levels compared with BDP. In a third long-term (1-year) comparative trial with FP, the authors concluded that there was little or no evidence of any important differences between equipotent FP and BDP in their effects on BMD or bone metabolism.⁵⁶

In addition, 2 prospective, blinded, placebo-controlled trials with FP have recently been reported. At the end of 2 years of FP treatment with 500 µg twice daily by Diskhaler, no statistically significant differences between FP and placebo were noted in BMD compared with baseline.⁵⁷ These adult subjects had documented, normal, baseline spine BMD at entry; BMD was monitored at 6-month intervals with quality assurance procedures. Osur et al⁵⁸ reported no significant differences in BMD from baseline in the 3 treatment groups (FP 88 µg twice daily with MDI and FP 440 µg twice daily with MDI vs placebo) at the end of 6 months. In both of these trials a normal response was defined as a bone-loss rate of change of less than 5% in the lumbar spine during the course of the study.

BUD 400 µg/day by Turbuhaler was compared with BDP 500 µg/day by MDI in a randomized, 2-year, prospective, open study⁵⁹; a nonsteroid reference therapy arm was included. No statistically significant differences in BMD were reported; 4 fractures occurred, which were evenly distributed between groups.

Bone effects: Conclusions

Earlier BMD data in patients with asthma taking inhaled corticosteroids were primarily retrospective analyses of poorly controlled studies. Either small effects on bone turnover or inconsistent results were reported; most studies were confounded by previous or concurrent corticosteroid use.

More recent prospective comparative or placebo-controlled studies with low and medium doses of BDP by chlorofluorocarbon propellant, FP, and BUD show little to no effect on BMD and metabolism. Unfortunately, comparably designed trials with BMD used as an outcome are not available with TA, flunisolide, or BDP by hydrofluoroalkane formulations. Patients requiring high doses of ICS for asthma control may be at long-term risk of bone loss, but likely to a much lesser extent than with maintenance oral corticosteroid therapy. Furthermore, because most studies excluded *a priori* individuals older than age 50 years or postmenopausal women to avoid the confounding influences of age and menopausal status on bone loss, the relative safety of ICS therapy in these susceptible populations is still unknown. For patients with severe persistent asthma requiring high-dose ICS therapy, FP and BUD appear to have superior therapeutic ratios to BDP.

EYE EFFECTS

The use of systemic corticosteroids is an established risk factor for the development of cataracts, particularly posterior subcapsular cataracts (PSCs). Cataracts are classified according to anatomic location; the most common types are cortical, nuclear, and posterior subcapsular. The most visually disabling type of cataract is the PSC, which accounts for most surgical lens extractions. Cortical and nuclear cataracts become a more frequent cause of vision loss with advancing patient age.⁶⁰

It is also well established that topical ophthalmic GCs can produce ocular hypertension and secondary open-angle glaucoma in susceptible individuals; most corticosteroid-induced cases of these eye disorders have resulted from topical ophthalmic administration. Adverse case reports with other routes of corticosteroid administration (eg, oral, periocular injections, eyelid creams or ointments, nasal, inhaled) have surfaced, raising concern in the asthma community.⁶¹

Population-based studies of ICS eye effects

Most available data on ICS eye effects consist of population-based, cross-sectional, or case-controlled studies. Specifically, 2 groups of investigators^{62,63} have conducted cross-sectional studies on ICS-treated children; in their studies no evidence of ICS-associated PSC was found. A large population-based, cross-sectional study in Australia recruited 3654 adults (age range, 49 to 97 years; median age, 65 years) for detailed eye examinations.⁶⁴ Three hundred seventy individuals self-reported current or previous use of ICS. Among these subjects, after adjusting for the influence of age and sex, there was a higher relative prevalence of nuclear cataracts and PSC than among the subjects with no ICS use. The prevalence of cortical cataracts, however, was not significantly higher. Higher cumulative lifetime doses of BDP were associated with higher PSC risk ($P < .001$). The associations with PSC but not those with nuclear cataracts were less marked when the analyses were restricted to subjects who never used systemic corticosteroids. The strengths of this study include the large sample size, high participation rate, control for confounding factors, and careful grading procedures of lens photographs. However, there are also some significant limitations. ICS use patterns (cumulative lifetime doses) were based on subject recall alone. The authors also acknowledged large amounts of missing data regarding both exposure-related variables and confounders. Analyses did not adjust for possible differences in occurrence of atopic disease, another potential confounding influence.

In a large case control study of Canadian health insurance enrollees (aged ≥ 66 years), 9793 case patients with a new diagnosis of borderline glaucoma or open-angle glaucoma were compared with 38,325 randomly selected patients in a control group.⁶⁵ Adjusted odds ratios (ORs) of ocular hypertension or open-angle glaucoma were determined. Current high-dose ICS users for ≥ 3 months were at increased risk of glaucoma (OR, 1.44; CI, 1.1 to 3.0). No significant increase in risk was observed in continuous users of low to medium doses of ICS. Because of the inherent restrictions in this study design, further controlled, prospective studies are required to confirm these observations.

Controlled, prospective studies of ICS eye effects

Prospective, controlled trials in both children and adults have included eye examinations as an additional safety outcome. Two previously described pediatric

TABLE VI. Preventive measures to minimize ICS adverse effects

General recommendations	
	Institute severity-appropriate ICS dosage regimens, with continual attempts to step down to minimal effective dose
	Consider combination pharmacotherapy (with long-acting β_2 -agonist or theophylline)
	Use spacer devices when appropriate
	Reinforce patient mouth-rinsing with water after ICS administration
Assessment for concurrent risk factors	
	Age
	Sex
	Pubertal status
	Dietary history (calcium, vitamin D)
	Sun exposure
	Smoking and alcohol history
	Physical activity level/immobility
	Concurrent diseases (eg, diabetes, thyroid disease, hypogonadism)
	Concurrent medication (eg, anticonvulsants)
Monitor patients at high risk with regular objective measurements	
	Oropharyngeal examinations
	Stadiometric height measurements
	Tanner sexual maturation staging
	Direct ophthalmoscopic examinations of the lens
	Bone mineral densitometry
Initiate specific interventions	
	Maintain adequate physical (ie, weight-bearing) activity
	Eliminate adverse health habits (eg, smoking, poor diet, sedentary lifestyle)
	Limit ultraviolet B exposure by wearing a hat and sunglasses
	Supplement diet with calcium/vitamin D
	Consider estrogen replacement therapy (or alternative pharmacologic strategies) to preserve bone mass

growth studies with BDP²³ and FP³² reported no evidence of ICS-related PSC or glaucoma. In 2 prospective placebo-controlled trials^{57,58} in adults treated with FP (500 μ g twice daily with Diskhaler and 88 to 440 μ g twice daily with MDI), no subjects had signs of glaucoma or PSC.

Eye effects: Conclusions

Both population-based and limited RCTs suggest that low- and medium-dose ICS regimens do not significantly contribute to the development of cataracts or glaucoma. These findings do not exclude the possibility that ICS, especially in high doses, can contribute to eye disease in individuals with high inherent susceptibility.

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS EFFECTS

Tests of adrenal function

Various adrenal function tests are available, each with a specific clinical implication. Adrenal function tests can either assess basal secretory functions (ie, morning cortisol levels, 24-hour cortisol profiles, 24-hour urinary free cortisol level) or involve stimulation testing (short or long versions). These tests have been reviewed extensively by Streeten et al.⁶⁶

Clinical relevance of HPA-axis effects

Recently, Dluhy⁶⁷ recommended that ICS HPA-axis effects must be carefully analyzed in regard to both defined study end points and clinical implications of the

findings. For example, although basal adrenal function can be sensitively measured and easily physiologically perturbed (over hours to days), clinically relevant suppression of the HPA axis with adrenocortical atrophy requires weeks or months of exogenous GC exposure. Even if moderate and high doses of exogenous corticosteroids affect the HPA axis, this rarely appears to be clinically significant. No cases of adrenal crisis have been reported in adults treated only with ICS⁴⁴; only case reports have been published in children.⁶⁸

Dluhy⁶⁷ has also reviewed factors influencing the incidence of adrenal suppression with ICS, which serve as potential confounding factors to accurate study analysis. These factors include dose and frequency of ICS administration, timing of ICS dose, duration of treatment, previous long-term systemic corticosteroid use, selected populations for study (eg, normal vs asthmatics, children vs adults), and significant interindividual variability.

HPA-axis effects of ICS therapy

The occurrence and magnitude of adrenal suppression are the most extensively evaluated systemic effects of ICS therapy and have been thoroughly reviewed in the literature.^{44,67} Most studies have concluded that at the low and medium dosage levels of marketed ICS products, the HPA axis is minimally and partially suppressed. It is only at high ICS dosage levels that the daily GC requirement is provided solely or exceeded by the ICS. The magnitude of this effect appears to be much less than prednisone doses of ≥ 10 mg/day.

HPA-axis effects: Conclusions

Studies of ICS effects on HPA-axis function in adults have been performed mainly to compare the systemic activity of different ICS preparations, often for marketing purposes. The clinical relevance of these studies is unknown. For example, in 2 pediatric growth studies with BDP that were able to detect growth velocity suppression,^{23,24} no alterations in cortisol measurements either at baseline or after stimulation were detected.

SUMMARY AND RECOMMENDATIONS

The spectrum of potential adverse effects with ICS is best studied in randomized, controlled, long-term clinical trials with the use of clinically relevant doses in patients with asthma severity and age similar to the groups in which the drugs would normally be prescribed. These studies must involve large numbers of subjects and by definition are difficult to conduct. Fortunately, more of these studies are becoming available.

Until sufficient definitive evidence is available with all marketed and future ICS preparations, clinicians must continue to implement preventive measures to minimize ICS adverse effects (Table VI). The National Asthma Education and Prevention Program guidelines should be followed with severity-appropriate ICS dosage regimens with continual attempts to "step down" therapy. Concurrent patient risk factors must be assessed, and "high-risk" patients should be monitored with validated objective measurements. Relevant lifestyle changes should be recommended and appropriate pharmacologic strategies implemented.

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