



February 1, 2002

Management Dockets
Dockets Management Branch
Food and Drug Administration
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Re: Draft Guidance for Industry: Evaluation of the Effects of Orally Inhaled and Intranasal Corticosteroids on Growth in Children
Federal Register 66(215):56109-56110 (November 6, 2001)
[Docket No. 01D-0432]
Comments for Consideration

Dockets Management:

Enclosed please find comments from GlaxoSmithKline on the draft guidance for industry entitled *Evaluation of the Effects of Orally Inhaled and Intranasal Corticosteroids on Growth in Children*. Notification of availability for comment on the guidance was published in the *Federal Register* on November 6, 2001 (Docket No. 01D-0432).

GlaxoSmithKline appreciates the opportunity to provide comments for consideration on the development of this guidance. While we have recommended some revisions to the proposed guidance, we fully support its development and look forward to working with the Agency to finalize a document which provides practical advice in the design, conduct, and interpretation of clinical trials to evaluate potential effects on growth in children who require prolonged treatment with orally inhaled or intranasal corticosteroids.

These comments are provided in duplicate. If you have any questions regarding these comments, please contact me at (919) 483-5211.

Sincerely,

Joy E. Ferrell
Senior Director
Regulatory Affairs

01D-0432

C3

Comments on the Draft Guidance for Industry:
Evaluation of the Effects of Orally Inhaled and Intranasal Corticosteroids on Growth in Children
[Docket No. 01D-0432]

1. General comment (cf. Lines 91-93, 156-159, 230-231)

Comment

While understanding the motivation behind the decision, we have some concern regarding the Agency's recommendation that for asthma, only mild persistent asthmatic subjects be studied. This concern is increased by the statement "Ideally, a range of doses should be studied if a dose range is approved or proposed..." There are two important reasons why we believe this is inappropriate. First, there are ethical issues with respect to administering higher doses of inhaled corticosteroids to patients than are clinically indicated. Second, for the same dose of inhaled corticosteroid, lung deposition is greater in patients with mild asthma compared with patients with more moderate or severe disease. This was confirmed in two recent studies (Saari et al. *Chest*. 1998;113(6):1573-1579, and Weiner et al. *Chest*. 1999;116(4):931-934.)

We believe that the entry criteria should more accurately reflect the intended population to whom the drug will be administered. This would allow for a more appropriate benefit risk assessment across the spectrum of the population who will be exposed to the specific agent. While the agency's guidelines reflect the potential for the 'worst case' scenario in milder patients, they also have the potential to exaggerate the effects of these drugs in the population of patients most likely to use them. More importantly, this does not allow an adequate assessment of the benefit risk ratio in patients with more moderate disease, those most likely to use these drugs.

Therefore, the information received from this type of study would not reflect the target population, and more seriously, may over-estimate treatment/dose effects.

2. Lines 50-54

Studies recently submitted to the Agency have demonstrated reduced growth velocities that were statistically significant (in the range of approximately 1 centimeter (cm) per year) among active treatment groups exposed to inhaled or intranasal corticosteroids as compared to control groups (placebo or noncorticosteroid asthma treatments such as beta-agonists).

Comment

As written, it is implied that the reduction of 1 cm is the rate seen per year for each year on corticosteroid therapy. Results from CAMP (*NEJM*. 2000; 343: 1054-1063) have shown a 1 cm reduction in the first year only, with the major effect observed within the first several months of initiating therapy. Other studies (Price & Weller. *Respir Med*. 1995;89:363-368, Agertoft & Pedersen. *NEJM*. 2000;343:1064-1069, Allen et al. *J. Pediatrics*. 1998;132 (3 Pt 1):472-477) have failed to confirm these effects, even in the 1st year.

3. Lines 80-82

Sponsors of both intranasal and inhaled corticosteroid products that contain the same active moiety may be able to use pharmacokinetic data to bridge the growth findings associated with one formulation to a second formulation.

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Comment

Pharmacokinetic data should only be used to bridge from one formulation to another if a PK/PD relationship between systemic exposure/growth or systemic exposure/cortisol/growth has been established for the compound of interest.

4. Lines 99-103

There should also be a follow-up period (preferably using a single-blind placebo or noncorticosteroid medications, as described above) to assess potential catch-up growth. The duration of the baseline period should be at least 16-weeks, the treatment period should be at least 48-weeks, and the follow-up period should be at least 8-weeks.

Comment:

We are of the opinion that a follow-up period of 8-weeks is too short to adequately evaluate catch-up growth. Furthermore, the growth results during the follow-up period may be confounded by the advancing age of this patient population, whereby the older patients may experience a pubertal/pre-pubertal growth spurt. Nonetheless, a 4-8 week follow-up period would be useful to evaluate if a change in Tanner staging has occurred.

Proposed new wording:

There should also be a follow-up period (preferably using a single-blind placebo or noncorticosteroid medications, as described above) to evaluate if a change in Tanner staging has occurred. The duration of the baseline period should be at least 16 weeks, the treatment period should be at least 48 weeks, and the follow-up period should be at least 4-8 weeks.

5. Lines 110-111

If the stadiometer has not been calibrated in the previous 4 hours, it should be calibrated immediately prior to measurement of patient height.

Comment

We question the need to recalibrate the stadiometer every 4 hours and suggest that a lapse of no more than 24 hours between calibrations is adequate. We suggest the Agency confer with manufacturers of stadiometers on the most appropriate re-calibration schedule.

6. Lines 113-117

The study design should incorporate practices that reduce measurement error. The investigators or examiners should be trained in stadiometry and calibration procedures. Ideally the same person should measure the children at every visit and should be blinded to the patients' status in the study.

Comment

Two additional practices that also have the potential to reduce measurement error are for height assessments to be performed at the same time of day for each patient throughout the course of the trial, and that the measurements at each timepoint be performed in triplicate, with the mean of the three measures taken. (Price, J. et al. "Evaluating the effects of asthma therapy on childhood growth. Part I: Principles of study design". Accepted for publication in *ERJ*.)

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Proposed new wording:

(to be added at end of line 117):

Measurements at each timepoint should be performed in triplicate, with the mean of the three measures taken as the height value for that time. In addition, measurements should be performed at the same time of day for each patient throughout the course of the trial. (Voss & Bailey. Archives of Disease in Childhood. 1997;77:319-322)

7. Lines 156-160 and 195-196

Lines 156-160

Patients included in growth studies with orally inhaled products should have a history of mild, persistent asthma for a minimum of 6 months prior to study entry. Patients should also have a documented percentage predicted FEV₁ ≥ 80 percent after withholding beta-agonists for ≥ 6 hours at both screening and first baseline visits.

Lines 195-196

Use of inhaled, intranasal or high potency topical corticosteroids within 6-weeks and systemic corticosteroids within 3 months of the first baseline visit.

Comment

We believe that the entry criteria should more accurately reflect the intended population to whom the drug will be administered. This would allow for a more appropriate benefit risk assessment across the spectrum of the population who will be exposed to the specific agent. While the agency's guidelines reflect the potential for the 'worst case' scenario in milder patients, they also have the potential to exaggerate the effects of these drugs in the population of patients most likely to use them. More importantly, this does not allow an adequate assessment of the benefit risk ratio in patients with more moderate disease, those most likely to use these drugs.

In order to include more moderate patients, we are of the opinion that eligible patients should have a documented percent predicted FEV₁ ≥ 60-70 percent after withholding beta-agonists for ≥ 6 hours at both screening and first baseline visits. Consistent with the inclusion of patients with mild to moderate asthma, patients may require short acting beta agonists alone, non-corticosteroid controller medications, or low doses of inhaled corticosteroids.

Proposed new wording:

Patients included in growth studies with orally inhaled products should have a history of mild or moderate persistent asthma for a minimum of 6 months prior to study entry. Patients should also have a documented percent predicted FEV₁ ≥ 60-70 percent after withholding beta-agonists for ≥ 6 hours at both screening and first baseline visits.

Use of high dose inhaled or intranasal corticosteroids or high potency topical corticosteroids for dermatological application within 6-weeks and systemic corticosteroids within 3 months of the first baseline visit.

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8. Line 187, with associated footnote (footnote 4)

Line 187

Baseline height velocity less than the 3rd percentile.

Footnote 4

The purpose of this criterion is to exclude patients with growth disorders from studies in which they may receive a growth-inhibiting drug. Baseline growth velocity can be calculated as a difference between the first and last baseline measurements or as a regression line using all the baseline measurements.

Comment

We recommend an exclusion criterion based on baseline height percentiles rather than baseline growth velocity percentiles. Normal growth velocity percentile curves are based on one-year of observational data. (Tanner & Davies. *J. of Pediatrics*. 1985;107(3):317-329). Hence, a 16-week run-in period will provide more variable estimates of growth velocity that precludes the use of these growth velocity percentile curves.

An exclusion criteria based on baseline height should also include an upper bound for exclusion (e.g., greater than 97th percentile). This will exclude patients at the extremes of the centile height ranges, as this may also be marker for a previously undiagnosed growth disorder. (Price, J. et al. "Evaluating the effects of asthma therapy on childhood growth. Part I: Principles of study design." Accepted for publication in *ERJ*. Duke, S. et al. *DIA*. 2000;34:397-409)

Proposed new wording:

To line 187: Baseline height less than the 3rd percentile or greater than the 97th percentile.

9. Lines 260-265

It is desirable that growth studies provide an estimate of treatment effect with a high level of precision (e.g., total length of 95 percent confidence interval 0.5cm). This level of precision should be attainable on the order of ≥ 150 completed patients per treatment group, using the design characteristics outlined in this document, and based on an analysis that controls for baseline growth velocity, age and gender in the model.

Comment

A potential issue with this recommendation is suggesting >150 completed patients. The high potential for dropout bias is well recognized and analysis of completers only data is not recommended in the guidance, so the sample size requirements should not be based on the number of completers. We recommend that the sample size requirement be worded in terms of randomized patients.

Based on the standard deviation reported in Duke 2000 (1.48cm/yr for the regression slopes using all patients), a sample size of 270 patients per treatment arm would be necessary to power a study to generate a 95% confidence interval with a total length of 0.5cm/yr. This sample size is considerably higher than what is proposed above. A sample size of 150

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patients per treatment group would provide of 95% confidence interval with total length approximately 0.7cm/yr using a within treatment group standard deviation of 1.48cm/yr.

10. Lines 275-278

The preferred measure of growth effects is the difference in growth velocity during the treatment period between active and placebo treatments. Individual patient growth velocities during the baseline, treatment and follow-up periods could be calculated using change from baseline in height or estimated using linear regression models.

Comment

Provided that missing data is 'missing at random', then we believe that an alternative statistical analysis method with increased power and precision is a random coefficients analysis. This method assigns less weight to patients with more variable data, which is likely to occur for patients with few data points due to early withdrawal. This method assigns more weight to patients with more data, and reduces the impact of confounders such as short-term variations in growth. The assumption of 'missing at random' may be more appropriate for studies evaluating the effects of intranasal corticosteroids on growth in children.

Proposed new wording:

The preferred measure of growth effects is the difference in growth velocity during the treatment period between active and placebo treatments. Individual patient growth velocities during the baseline, treatment and follow-up periods could be calculated using estimated linear regression models and an ANCOVA then performed. Alternatively a random coefficients model could be implemented if the number of patient withdrawals were low and the assumption of missing-at-random missingness is deemed to be reasonable.

11. Lines 278-281

An ANCOVA model involving all randomized patients with at least three recorded height measurements during the double-blind treatment period is recommended to estimate the mean difference between treatment groups in growth velocity over the treatment period.

Comment

Stipulating that patients must have at least three on-treatment height measurements is in disagreement with intention-to-treat principles, where all randomized patients are included. Additionally, this analysis would introduce a bias caused by ignoring the data from patients withdrawing prior to obtaining three on-treatment measurements. In order to draw inferences about the population randomized, as many patients as possible need to be included in the analysis, and having one post-baseline observation is sufficient to do this.

Proposed new wording:

An ANCOVA model involving all randomized patients with at least one post-baseline measurement is recommended to estimate the mean difference between treatment groups in growth velocity over the treatment period.

12. Lines 320-322

It is recommended that pulmonary function tests be performed at every office visit.

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Comment

We are of the opinion that while it is optimal to perform an FEV₁ in all patients, there will be a significant proportion of patients in whom a meaningful FEV₁ will not be obtainable. In these patients, we propose that the use of a peak expiratory flow rate (PEF) with similar entry criteria will suffice. Because the primary objective of this study is not to evaluate efficacy, we propose that FEV₁ or PEF should be obtained in the office at 12-week intervals throughout the treatment period.

Proposed new wording:

It is recommended that spirometry (or peak expiratory flow rate in those patients unable to perform spirometry) be performed at office visits at least every 12-weeks during the treatment period.

Regional Lung Deposition and Clearance of ^{99m}Tc-Labeled Beclomethasone-DLPC Liposomes in Mild and Severe Asthma*

S. Marisanna Saari, MD; Mika T. Vidgren, PhD; Matti O. Koskinen, PhD; Väinö M.H. Turjanmaa, MD, PhD; J. Clifford Waldrep, PhD; and Markku M. Nieminen, MD, PhD

Objective: To compare the distribution and clearance of inhaled beclomethasone dipropionate (Bec)-dilauroylphosphatidylcholine (DLPC) liposomes in patients with mild and severe asthma. **Design:** A ^{99m}Tc-labeled Bec-DLPC suspension was delivered via a nebulizer (Aerotech II). Immediately after inhalation, anterior and posterior views of the lungs and an anterior view of the oropharynx were measured by a large field gamma camera with the patient in a supine position. To evaluate the mucociliary clearance of the inhaled liposomes, anterior and posterior lung scans were repeated 1, 2, 4, and 24 h after the aerosol delivery.

Patients: Ten patients with mild asthma (FEV₁ >80% of the predicted) and 10 patients with severe asthma (FEV₁ <60% of the predicted) were included in an open, parallel group study.

Results: Clearance is more rapid among patients with severe asthma (p<0.0001). At the 4-h measurement, a mean of 82% (SD, 5.9) of the total pulmonary dose was detected in the lungs of patients with mild asthma while in those with severe asthma the figure was 69% (SD, 10.9). The ratio between central and peripheral deposition was significantly higher for patients with severe asthma than for those having a mild form of the disease; 1.07 (SD, 0.29) and 0.76 (SD, 0.07), respectively (p=0.008).

Conclusions: Inhaled Bec-DLPC liposomes were deposited more centrally in the lower airways of patients with severe asthma than those having a milder form of the disease. The clearance of Bec-DLPC liposomes is strikingly slow in both groups of asthmatic patients. However, due to the more peripheral penetration of inhaled liposomes in patients with mild asthma, the clearance rate in this group was slower than in those with severe asthma.

(CHEST 1998; 113:1573-79)

Key words: aerosol; asthma; beclomethasone dipropionate (Bec); corticosteroids; dilauroylphosphatidylcholine (DLPC); liposome; nebulizer; ^{99m}technetium

Abbreviations: Bec=beclomethasone dipropionate; Bec-DLPC=beclomethasone dipropionate-dilauroylphosphatidylcholine; C=central; DLPC=dilauroylphosphatidylcholine; DPPC=dipalmitoylphosphatidylcholine; ITLC=instant thin-layer chromatography; MMAD=mass median aerodynamic diameter; P=peripheral; ROI=region of interest

The administration of drugs by inhalation is an effective means for delivering relatively small quantities of therapeutics to target sites. Neverthe-

less, most drugs are rapidly cleared from the lungs and pass into the systemic circulation. This explains the relatively short therapeutic effect of inhaled drugs, the necessity for frequent dosages, and the occurrence of unwanted systemic side effects.

Liposomes are a carrier system for pulmonary drug delivery currently under wide investigation. They seem to be particularly appropriate drug carriers, as they can be prepared from phospholipids present endogenously as components of pulmonary surfactant in the respiratory tract. Recent studies of pulmonary deposited liposomes have indicated that liposome encapsulation of a drug before administration can prolong the presence of the inhaled drug in lower airways¹ and limit rapid redistribution to other

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tissues.² In addition, a decreased incidence of systemic side effects of intrapulmonary-administered liposome-encapsulated drugs has been reported.³

Recently, synthetic droplet size liposome aerosols have been developed for the treatment of pulmonary disorders such as bronchial asthma. A previous study demonstrated that beclomethasone dipropionate (Bec)-dilauroylphosphatidylcholine (DLPC) liposome aerosols can be administered into the lower airways via several different nebulizers.⁴ In addition, the tolerability and pulmonary deposition of Bec-DLPC liposomes have been studied in healthy volunteers.⁵⁻⁷ However, there are no data on the deposition and clearance of Bec-DLPC liposomes in asthmatic patients to date, and to our knowledge.

The objective of this study was to compare the distribution and clearance of inhaled Bec-DLPC liposomes in patients with mild and severe asthma after administration with a jet nebulizer (Aerotech II; CIS-US, Inc; Bedford, Mass).

MATERIALS AND METHODS

Subjects Studied

Twenty adult nonsmoking patients (age >18 years) with stable chronic asthma were included in an open, parallel group study. They were recruited from the outpatient clinic of the Department of Pulmonary Diseases of Tampere University Hospital.

All diagnoses were based on clinical evaluations by the attending chest physician and fulfilled the criteria defined by the American Thoracic Society⁸ with the addition of an increase in FEV₁ >15% following a bronchodilation test (the inhalation of 200 µg of salbutamol from a metered-dose inhaler). All patients had had the disease for at least 6 months. Ten patients had a mild form of asthma and 10 had a severe form of asthma. The patients with mild asthma were five women and five men with a mean age of 49 years (range, 32 to 60 years), while those having a severe form of the disease were also five women and five men with the mean age of 57 years (range, 47 to 66 years). Baseline FEV₁, measured immediately prior to the experiment, was 80% of the predicted in those with mild asthma, and 60% of the predicted in those having severe asthma (Table 1).

At the beginning of the study, medical histories were taken and physical examinations were carried out by the attending pulmonary physician. None of the subjects had an exacerbation of their asthma or an upper respiratory viral infection within the previous

4 weeks. Moreover, patients with any other significant pulmonary or cardiac disease or those having β-blocker, calcium channel blocker, angiotensin-converting enzyme inhibitor, or oral β₂-agonist therapy were excluded. Patients abstained from inhaled long-acting β-agonists (salmeterol or formoterol) for at least 24 h, oral controlled-release theophylline preparations for at least 48 h, caffeine-containing beverages for 12 h, and inhaled corticosteroids and shortacting bronchodilators for at least 8 h prior to the study. Oral corticosteroid treatment with one patient continued unchanged. After the trial, patients continued taking their asthma medication as previously prescribed.

The study was conducted according to the Declaration of Helsinki. Written, informed consent was obtained from all patients, and the study protocol was approved by the Ethical Committee of Tampere University Hospital.

Labeling of Bec-DLPC Liposomes With ^{99m}Tc

Bec and DLPC liposomes were produced as previously described.⁹ Briefly, 1 mg Bec and 25 mg DLPC were dissolved in 10 mL t-butanol. After mixing, the Bec-DLPC solution was pipetted into glass vials, rapidly frozen in dry ice-acetone, and lyophilized overnight to remove the organic solvent. The liposome suspension was produced by adding ultra-pure water to obtain a final drug concentration of 500 µg/mL. The mixture was stirred for 30 min at 37°C to allow hydration of the liposomes.

The preformed Bec-DLPC liposomes were labeled with Tc in the presence of SnCl₂ as a reducing agent. In the preparation of a stannous chloride solution, it is important to exclude the possibility of oxidation of tin to the nonreactive stannic form. Therefore, before dissolving stannous chloride (67 mg), 100 mL of sterile, pyrogen-free water was bubbled 30 min with nitrogen in order to expel most of the oxygen. Then 1 mL of Tc pertechnetate in sterile saline solution, with a radioactivity of approximately 780 MBq (21 mCi), was added, and the mixture (total volume, 2.5 mL) was shaken vigorously for 1 min and left to react at room temperature for 30 min.

Assessment of ^{99m}Tc Attachment to Liposomes

The radiochemical purity of liposomes was determined after every labeling by instant thin-layer chromatography (ITLC). In the two-strip mini-ITCL procedure,¹⁰ normal saline solution was used as a solvent and silica gel (ITCL-SG, prod. 61885; Gelman Sciences; Ann Arbor, Mich) as an absorbent in order to measure the amount of free ^{99m}Tc.

Micropartitioning and the chromatographic analysis of labeled Bec-DLPC liposomes have demonstrated a high labeling efficiency (96 to 99%) with minimal free Tc.⁶ The SnCl₂-catalyzed reduction of Tc⁴⁺ ions reacts primarily with the phosphate portion of the DLPC, forming a positive and stable association between the radioactive tag and the liposome. A cascade impaction analysis (Anderson cascade impactor) was performed earlier in order to examine the quantities of Bec, DLPC, and Tc in different particle size fractions, and the extent to which the amount of radioactivity corresponded to the amount of Bec and DLPC.⁶ The analysis showed a positive correlation among Bec, DLPC, and ^{99m}Tc in the aerosol particles. The correlation coefficient of Bec and ^{99m}Tc concentrations at different stages of the cascade impactor also showed a positive correlation. The mass median aerodynamic diameters (MMAD) and the geometric standard deviation of Bec-DLPC liposomes were 1.5/2.3, 1.4/2.2, and 1.7/1.8 according to the drug, radioactivity, and lipid analyses, respectively, after administration from the nebulizer (Aerotech II) using an airflow of 10 L/min.

Although the liposomes were labeled before nebulization, the

Table 1—Patient Characteristics in Mild and Severe Asthmatic Groups

Characteristics	Mild Asthma (n=10)		Severe Asthma (n=10)	
	Mean	SD	Mean	SD
Sex, M/F	5/5		5/5	
Age, yr	49.1	8.5	55.2	6.4
FVC, % of predicted	98.2	11.5	66.9	19.8
FEV ₁ , % of predicted	90.1	6.7	47.6	16.0

reduction of initial particle size by the nebulizer did not cause any disintegration of the bond between the phospholipid and the radioactive tag. Thus, the ^{99m}Tc remained associated with the Bec-DLPC liposomes during nebulization and in the aerosol particles with a homogenous distribution of the radioactive tag throughout the lipid phase.

Corticosteroid-Liposome Delivery

The Tc-labeled Bec-DLPC suspension was delivered from nebulizers (Aerotech II) connected to an automatic, inhalation-synchronized dosimeter (Spira Elektro 2; Respiratory Care Center; Hämeenlinna, Finland). This dosimeter is triggered by a very low inspiratory flow rate with a threshold of <2 L/min.¹¹⁻¹³ The volume of each inhalation is displayed digitally, and the inhalation flow rate is controlled by a flow indicator. A breath-actuated, variable-time circuit regulates air through a solenoid valve to a nebulizer, set at a flow rate of 10 L/min. The volume output of the dosimeter with 0.5-s nebulization periods under these operating conditions is 7 μL per breath (SD, 0.5).¹¹⁻¹³ In this study, the dosimeter was set to start nebulization in the beginning of the inhalation after the patient had inhaled a volume of 10 mL, with each inhalation lasting approximately 3.0 s.

A total dose of 500 μg Bec within the labeled liposomes (2.5 mL), having an initial radioactivity of approximately 780 MBq (21 mCi), was placed in the jet nebulizer. Subjects were instructed to place the nebulizer tightly between their lips and inhale deeply. With a noseclip and mouthpiece in place, the subject controlled breathing with a flow indicator (an LED screen) so that the inspiratory flow rate of each breath reached but did not exceed 30 L/min. Inhalation was followed by normal exhalation. Exhaled Bec liposomes were captured using a filter (Hudson; Temecula, Calif). This inspiration procedure was repeated 20 times according to the subject's own inspiratory cycle with no holding of breath between inhalations. Nebulization was practiced by each subject with saline solution before the experiment began.

In addition, spirometric measurements (Vitalograf; Buckingham, UK) were performed before inhalation of the Bec-DLPC suspension. At least three technically correct maneuvers for forced maximal expiratory flow-volume curves were performed, and the curve with the greatest sum of FEV₁ and FVC was utilized in obtaining data for the patient's characteristics.

Gamma Camera Measurements

Immediately after inhalation, anterior and posterior views of the lungs and an anterior view of the oropharynx were measured with the patient in a supine position by a large field gamma camera (GE; CamStar XR/T; Waukesha, Wis) equipped with a low-energy high-resolution parallel collimator. To evaluate the mucociliary clearance of the inhaled liposomes, scans were repeated 1, 2, 4, and 24 h after the aerosol delivery. In addition, a posterior ventilation scan was obtained after the liposome study by inhaling noble gas ^{133}Xe with a radioactive dose of 460 MBq (12.5 mCi). All images were stored on computer (Hermes; Nuclear Diagnostics; Hägersten, Sweden) for subsequent data analysis. The gamma camera pictures, with different imaging points, are illustrated in Figure 1.

^{133}Xe posterior images were used when regions of interest (ROI) were drawn manually around central (C) and peripheral (P) lung zones. ROIs were subsequently superimposed on each liposome aerosol view, enabling the quantity of aerosol dose in each of the zones to be determined. Each image was aligned manually, *ie*, each lung view was moved to adapt to the superimposed ROIs. The lungs were divided into inner and outer region, with the inner zone encompassing 33% ($\pm 2\%$) and outer the rest of the total lung area.^{11,15} Lung distribution of the liposome aerosol was described as the ratio between C and P lung areas (C/P ratio) and the total lung clearance curve as a plot of the percentage of initial lung burden vs time after inhalation. Additionally, ROIs were drawn around the oropharynx, the chest, and the abdomen (Fig 2). Total counts, measured from the oropharynx and body regions, represented the total combined amount of radioactivity of the subject.

The number of counts and pixels in each ROI was measured and saved on a file of the computer (Hermes). Subsequently, the data were transferred via a local area network to a personal computer and analyzed with a program specially made for this study. Counts from the anterior and posterior views of the lungs were combined by taking geometric mean values. The camera-to-patient distance was standardized by placing the collimator close to the chest for the anterior view and in contact with the imaging bed for the posterior view. Geometric mean counts were corrected for the room's background—measured separately from each image—and for radioactive decay.

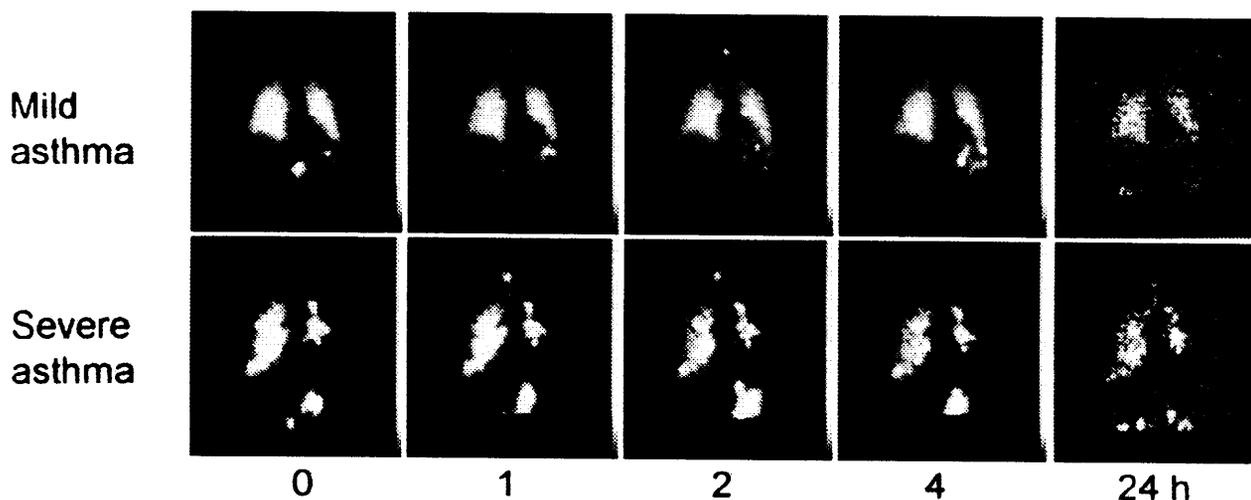


FIGURE 1. Anterior chest scintigraphs of a patient with mild asthma and a patient with severe asthma at 0, 1, 2, 4, and 24 h following ^{99m}Tc -labeled Bec-DLPC liposome aerosol. The images are corrected for background and physical decay.

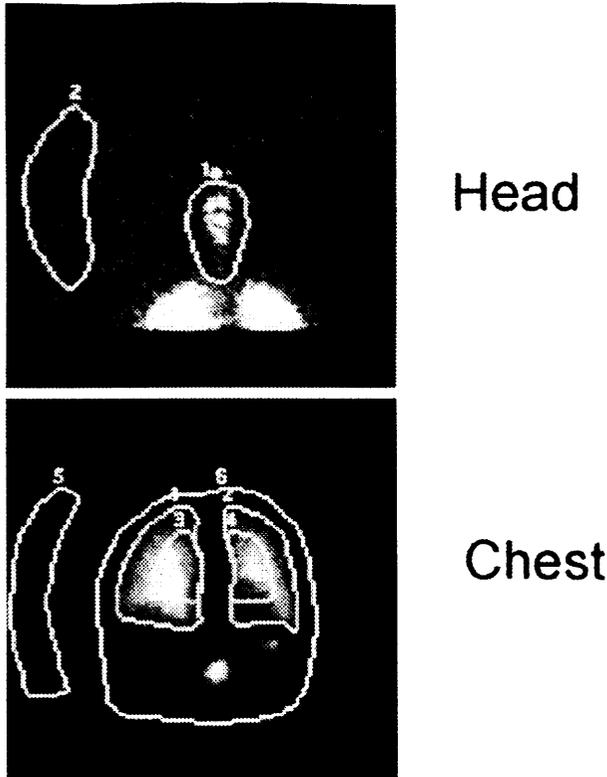


FIGURE 2. ROIs manually drawn around the oropharynx, body region, C and P lung zones in both lungs and the background.

An approximate tissue absorption correction was carried out by using the method described by Macey and Marshall.¹⁶ Briefly stated, prior to the liposome study, individual transmission images of each subject's oropharynx and lung region were taken using a flat radiation source and keeping the imaging geometry similar both in transmission and ventilation scans. This transmission method was used to correct the individual emission counts recorded with the gamma camera.

Radioactivity in the nebulizer reservoir was measured before and after inhalation with a dose calibrator (Capintec; Ramsey, NJ). In addition, the filter collecting exhaled liposomes was measured. Mean activity was calculated to be 19 MBq in the lungs and 25 MBq in the whole body.

Statistical Analysis

An unpaired *t* test was used to study differences between the asthma groups at the baseline and after 24 h. For gamma camera measurements, consisting of repeated observations within the study day, analysis of variance for repeated measurements was applied to study between-group differences, changes during the recording period, and interaction between groups and recording periods.

RESULTS

There were no differences in the demographic data between the two groups of asthmatic patients as demonstrated in Table 1. The mean values of FEV₁

as percentages of the predicted values were 47.6 (SD, 16.0) and 90.1 (SD, 6.7) for patients with mild and severe asthma, respectively (Table 1).

ITLC was done after every labeling process of liposomes. ITLC analysis showed a significantly high labeling efficiency (97 to 99%).

The regional deposition pattern of ^{99m}Tc Bec-DLPC liposomes is demonstrated in Figure 1. In patients with mild asthma, there was a uniform distribution of counts within the C and P lung fields. In contrast, in patients with severe asthma, there was an asymmetric distribution of increased numbers of counts associated with central airways.

Fractional distribution patterns of ^{99m}Tc Bec-DLPC liposomes after inhalation in patients with mild and severe asthma are seen in Figure 3. The percentage of the delivered dose deposited in the lungs in patients with severe asthma (68%) was similar to that of patients with mild asthma (66%). The combined values of oropharyngeal and GI deposition in both groups were very similar, being 20% and 23%, respectively.

Figure 4 shows a progressive clearance of ^{99m}Tc Bec-DLPC in both groups during the 24-h period. However, clearance is more rapid among patients with severe asthma (*p* < 0.0001). At the 4-h measurement, a mean of 82% (SD, 5.9) of the total pulmonary dose was detected in the lungs of patients with mild asthma, while in patients with severe asthma, the figure was 69% (SD, 10.9).

After 24 h, 72% and 54% of the initial liposome dose was still detected in the whole lung area, respectively. During the entire 24-h follow-up, neither group reached 50% of the initial lung dose.

Results concerning regional pulmonary deposition are given in Figure 5. Immediately after liposome inhalation, the ratio between C and P deposition

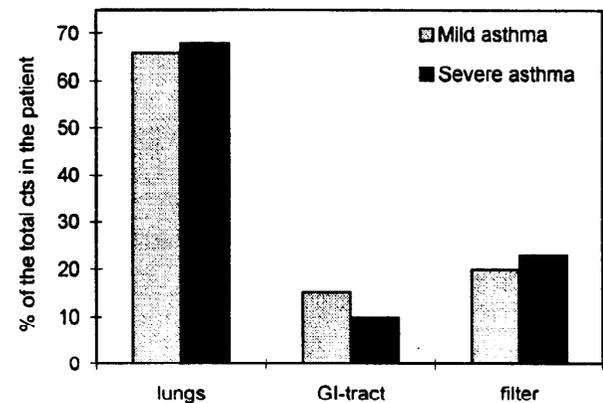


FIGURE 3. Fractional distribution (percent) of ^{99m}Tc delivered from the Aerotech II nebulizer following inhalation of Bec-DLPC liposome aerosol.

DISCUSSION

Inhaled liposome corticosteroids are expected to be a major next step in the development of inhaled anti-inflammatory asthma therapy. Novel compounds have recently advanced to phase III clinical trials, and this therapy may be registered for routine asthma treatment by the end of the millennium.

To our knowledge, the present study was the first to study liposome-corticosteroid airway deposition and clearance in asthmatic patients. By using a computer model, Waldrep et al⁹ previously estimated that Bec-DLPC liposome deposition would be greatest in the lung periphery, with less predictable deposition in the upper areas of the respiratory tract. This hypothesis was now confirmed in our study among asthmatic patients showing a high total pulmonary deposition of inhaled liposomes (66 to 68% of the delivered dose), whereas the mouth and throat retention in both groups was low. These data are in accordance with the results of Dahlström and Larsson,¹⁷ who showed in normal subjects that on average, 64% of a nebulized liposome-free budesonide suspension (Pulmicort Turbuhaler; Astra USA; Westborough, Mass) with an MMAD of 3 μm could be inhaled into the lungs. Furthermore, by relating the pulmonary deposition to the nominal dose (=dose placed into the reservoir), on average, 15% was deposited into the whole lung area. These results are similar to previously obtained data by Vidgren et al⁶ concerning Bec-DLPC liposomes (17%, MMAD 2.1 μm) in healthy volunteers. Thus, when comparing the numeric values presented in different deposition study reports, it is important to characterize not only the patient population, drug delivery system, and mode of inhalation, but also the basis for percentile calculations of pulmonary deposition (nominal/delivered dose).

In our study, the (Aerotech II) jet nebulizer we used was chosen for liposome delivery because it produces aerosols likely to result in the alveolar deposition of inhaled liposomes (MMAD approximately 2 μm). In addition, the slow inspiratory airflow was used to minimize impaction in the upper parts of the respiratory tract. It has been stated that with radioaerosols, the magnitude of bronchial obstruction is a determinant of aerosol distribution within the lungs of patients with asthma, and that increased bronchial obstruction enhances central airway deposition of inhaled particles.¹⁸ It has also been shown that FEV₁ predicts, to a high degree, the penetration of the peripheral zone of the lungs, where a lower FEV₁ is associated with less peripheral penetration.¹⁹ Accordingly, in mild asthma, the distribution of pulmonary deposition is more centralized than among normal subjects^{20,21} while in pa-

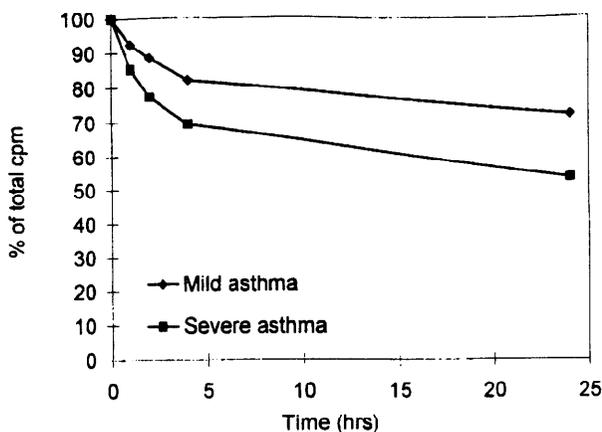


FIGURE 4. Clearance of ^{99m}Tc from the lungs of patients with mild and severe asthma following inhalation of ^{99m}Tc-labeled Bec-DLPC liposome aerosol.

(C/P ratio) in patients with severe asthma was significantly higher than in those having a mild form of the disease: 1.07 (SD, 0.29) and 0.76 (SD, 0.07), respectively ($p=0.008$). Thereafter, only a slight decline in the difference was found during the follow-up period while retaining the marked significance between the two groups at 24 h, 0.76 (SD, 0.17) vs 0.67 (SD, 0.05) ($p<0.001$).

Adverse Effects

The only adverse effect detected was nausea in two patients with severe asthma immediately after inhalation of Bec-DLPC liposomes. Another patient experienced mild vomiting a few minutes after liposome inhalation.

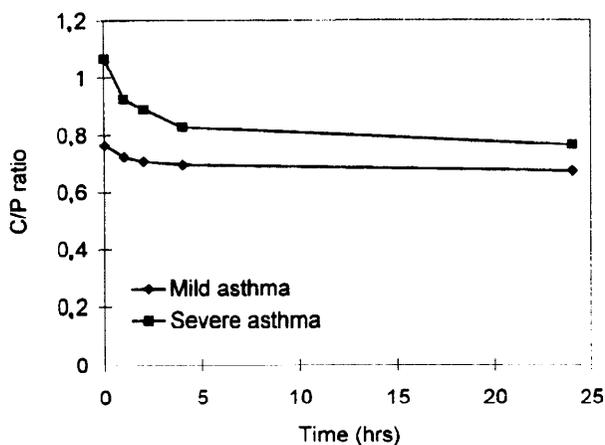


FIGURE 5. C/P ratio as a function of time in mild and severe asthma following inhalation of ^{99m}Tc-labeled Bec-DLPC liposome aerosol.

tients with severe asthma, it is even more proximal. Nonuniform deposition in lung scans of patients with severe asthma represents the asymmetric nature of disease and subsequent narrowed airways as similarly noted for patients with bronchiolitis obliterans.²² The results of our study correspond well with previously published data.

In previous studies, the clearance of original liposome-associated ^{99m}Tc has proved to be strikingly slow.^{6,23,24} Vidgren et al⁶ observed the clearance of ^{99m}Tc Bec-DLPC of healthy volunteers. After 3 h, 93% of the original dose was still detected in the lungs. In a similar study, Farr et al²³ measured deposition and clearance of dipalmitoylphosphatidylcholine (DPPC) liposome aerosol after inhalation by normal volunteers. Subjects were monitored for 6 h after inhalation and 88% of inhaled radioactivity was still present in the lungs. Barker et al,²⁴ have recently studied liposome (DPPC) entrapped ^{99m}Tc-DTPA and demonstrated that approximately 45% of originally deposited radioactivity remained in the lungs after 24 h. This represented the fraction of the radiolabel remaining intact on alveolar-deposited vesicles, since free ^{99m}Tc-DTPA was moved from the airways with the half-life of 75 min.

In our study, the clearance of original liposome-associated ^{99m}Tc was strikingly slow and the clearance kinetics were similar in both groups of asthmatic patients. However, due to the more peripheral penetration of inhaled liposomes in patients with mild asthma, the clearance rate was somewhat slower than among those with severe asthma.

Impaired mucociliary clearance in asthma has been detailed in various studies.^{20,21,25-27} However, in our data, the clearance of Bec-DLPC liposomes was faster among patients with severe asthma than among patients with mild asthma. This difference is likely due to the site of the deposition of liposome vesicles in the respiratory tract. The significantly higher C/P ratio immediately after inhalation in patients with severe asthma indicates both a greater degree of centrally deposited liposome vesicles and of liposomes cleared through mucociliary escalation. In patients with mild asthma, a greater portion of the inhaled liposome aerosol penetrated into the alveolar region, where removal of the particles by absorption and phagocytosis of the macrophages is markedly slower.

Two patients with severe asthma felt nausea immediately after inhalation of Bec-DLPC liposomes. The clinical impression was that both patients hyper-ventilated during inhalation and the occurred side effects were due to the exhaustion from the inhalation. In previous studies with the similar Bec-DLPC concentration, no adverse effects were reported.^{6,7}

As mentioned above, there are great expectations

for the future regarding inhaled liposome corticosteroids in asthma therapy. They might permit once daily or even more infrequent steroid inhalation, while yielding fewer local and systemic side effects and better patient compliance. Today, however, rather limited information concerning the retention of the steroid in the liposome matrix in lower airways exists. A key issue is the lipophilic properties of the steroid component, which directly relates to the retention of the steroid in the liposome matrix of the complex. In the present study, we radiolabeled only the phospholipid part of the complex. Therefore, one must interpret with caution the present data with regard to treatment.

In conclusion, the radioisotope method enables the study of the deposition and clearance of inhaled liposome preparations for various respiratory disorders. In this study, impaired pulmonary function led to a more centralized deposition of aerosolized corticosteroid liposomes and, as a consequence of mucociliary escalation, faster pulmonary clearance of the inhaled liposomes.

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Nocturnal Cortisol Secretion in Asthmatic Patients After Inhalation of Fluticasone Propionate*

Paltiel Weiner, MD; Noa Berar-Yanay, MD; Avi Davidovich, MD; and Rasmi Magadle, MD

Objectives: This study was designed to assess the relationship between the degree of airflow obstruction and the suppression of the hypothalamic-pituitary-adrenal axis after inhalation of fluticasone propionate (FP) in asthmatic patients with varying degrees of airway obstruction.

Study design: The nocturnal cortisol production (from 10:00 PM to 6:00 AM), defined as the integrated area under the curve of nocturnal plasma cortisol, was measured following inhalation of a placebo or a single dose of 500 µg FP at 8:00 PM in 28 patients with mild to moderate asthma, in a single, blind, 2-night study.

Results: The mean morning rise of cortisol decreased significantly following a single dose of inhaled FP. When the total nocturnal cortisol production after the second night (when the FP was inhaled) was compared to that after the first night (when the placebo was administered), it was found to have decreased by 29.4%. There was a statistically significant correlation between the FEV₁ and the fall in cortisol production just before the inhalation of FP ($p < 0.001$). There was no correlation between baseline cortisol production and the fall in cortisol production.

Conclusions: Our findings suggest that the degree of airway obstruction affects the systemic bioavailability of FP. FP is likely to induce a more severe decrease in nocturnal cortisol secretion in less obstructed patients. In order to reduce the risk for systemic side effects, the patient's degree of airway obstruction should be considered when planning inhaled FP treatment.

(CHEST 1999; 116:931-934)

Key words: airway obstruction; asthma; inhaled glucocorticoids

Abbreviations: AUC8h = the integrated area under the curve of nocturnal plasma cortisol; FP = fluticasone propionate; HPA = hypothalamic-pituitary-adrenal axis; IGC = inhaled glucocorticoids

Inhaled glucocorticoids (IGC) are highly efficacious in the treatment of asthma,¹ but some questions about this treatment modality remain unanswered, such as the potential for growth suppression in children and the potential for adrenal suppression and osteoporosis in both children and adults.

Certain data suggest a possible dose-response relationship with regard to IGC therapy.²⁻⁵ These studies have shown that dose-dependent suppression of the hypothalamic-pituitary-adrenal axis (HPAA) occurs in healthy volunteers and in asthmatic patients even following a single-dose inhalation of IGC.

Systemic bioavailability of IGC is mainly determined by absorption of the drug across the lung vascular bed.^{6,7} Consequently, lung deposition and

systemic bioavailability might be altered by the narrowed airway caliber in patients with asthma. Peripheral lung deposition has been found to be significantly higher in normal subjects than in asth-

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tics inhaling salmeterol.⁸ We hypothesized that the degree of HPA suppression in asthmatic patients is inversely related to the degree of airflow obstruction following the inhalation of corticosteroids.

MATERIALS AND METHODS

Patients

Twenty-eight patients with mild to moderate asthma were studied. The patients satisfied the American Thoracic Society definition of asthma, with symptoms of episodic wheezing, cough, and shortness of breath responding to bronchodilators, and reversible airflow obstruction documented in at least one previous pulmonary function study.⁹ Patients who received oral or inhaled corticosteroids in the last 3 months were excluded from

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the study. All patients were on rescue treatment with β_2 -agonists only. The patients were not allowed to use β_2 -agonists 12 h before entering the study and during the study. The characteristics of the patients are summarized in Table 1. The study was approved by the institutional committee on human research, and informed consent was obtained from all patients.

Study Design

This study was designed as a single, blind, 2-night study in which, during the first night, the baseline integrated area under the curve (AUC_{8h}) of nocturnal plasma cortisol was measured following the administration of the placebo using an inhaler (Diskhaler; Glaxo Wellcome Group; Uxbridge, Middlesex, UK), and during the second night, AUC_{8h} was measured following inhalation of a single dose of 500 μ g of fluticasone propionate (FP) by way of an inhaler (Diskhaler; Glaxo Wellcome Group). The patients were instructed to hold the inhaler away from their mouths, to exhale as far as they could, to inhale through the mouthpiece steadily and as deep as they could, and to hold their breath as long as possible. On each night, pulmonary function tests were performed following insertion of an indwelling cannula into a forearm vein in order to ensure venous access during the night without disturbing sleep. A single evening dose of an inhaled placebo (day 1) or FP (day 2) was administered at 8:00 PM, and blood samples for cortisol were taken every hour from 10:00 PM to 6:00 AM.

The FP and the placebo were administered using a standard inhaler with 500 μ g per inhalation. Before enrollment, all participants were instructed carefully on the use of the inhaler.

Tests

Spirometry: The FVC and the FEV₁ were measured three times on a computerized spirometer (Compact; Vitalograph; Buckingham, UK), and the best trial is reported. Spirometry was performed just before the inhalation of either the placebo or the FP. Cortisol was measured using an automated system based on a solid-phase chemiluminescent enzyme immunoassay (IMMULITE system; Diagnostic Products; Los Angeles, CA).

Data Analysis

The nocturnal cortisol production was calculated as the area under the curve using Simpson's rule for data points spaced equidistantly.

Table 1—Patient Characteristics*

Characteristics	Data
Patients	28
Age, yr	
Mean	32
Range	18–43
Sex	
Female	12
Male	16
Asthma severity	
Mild	11
Moderate	17
Smokers	2
Nonsmokers	26
Mean FEV ₁ , % predicted, L	
Before placebo	73.4
Before FP	71.3

*Data are expressed as No. unless otherwise indicated.

To compare the results obtained the night the placebo was used to the results obtained the night the active drug was used, the percent changes of cortisol production were analyzed using the Mann-Whitney *U* test.

RESULTS

FEV₁ ranged from 42 to 96% of predicted normal values (mean \pm SEM, 71.3 \pm 2.9%) before the administration of FP. These data did not differ from the results obtained just before the inhalation of the placebo during the beginning of the first night.

The mean cortisol levels during the 2 nights of the study are displayed in Figure 1. A single dose of inhaled FP from the second night had a considerable effect on the early morning rise of cortisol secretion. When the nocturnal cortisol production after the second night was compared to that after the first night (when the placebo was administered), the total nocturnal cortisol production, calculated as AUC_{8h}, was found to have significantly reduced by 29.4%. The individual changes in the nocturnal cortisol production are shown in Figure 2. There was a statistically significant correlation between the FEV₁ measured just before the inhalation of FP and the fall in cortisol production ($p < 0.001$; Fig 3). There was no correlation between the FEV₁ prior to the placebo and baseline cortisol production (as expressed by the AUC_{8h} during the first night) or between the baseline cortisol production and the decrease in cortisol production during the second night.

DISCUSSION

This study has shown that in asthmatic patients, a single inhalation of FP causes a significant reduction in nocturnal AUC_{8h} plasma cortisol. This reduction

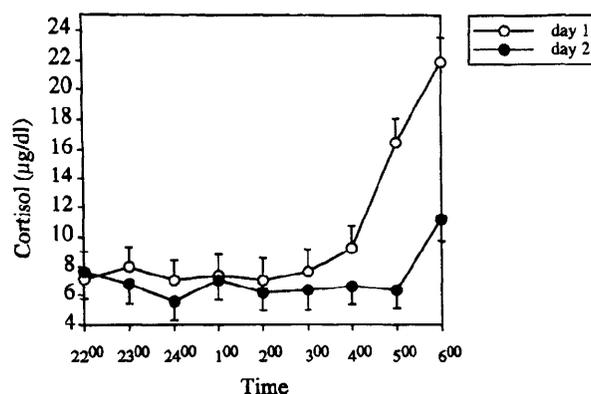


FIGURE 1. Mean \pm SEM blood cortisol concentrations during the 2 nights of the study: day 1 when the placebo was administered and day 2 when 500 μ g FP was inhaled at 8:00 PM.

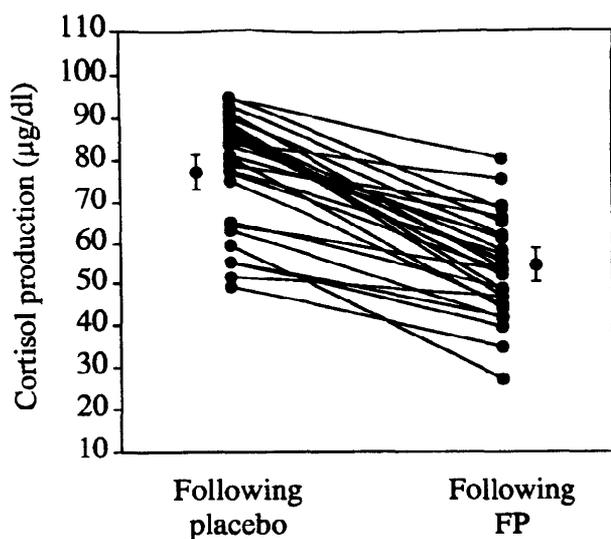


FIGURE 2. The individual data of nocturnal cortisol production following inhalation of placebo and FP.

was inversely correlated with the patient's airway obstruction. The data suggest that there is a dose-response relationship with regard to the efficacy of IGC, at least in terms of conventional dosing regimens.^{2,3,10} IGC are generally regarded as safe at low doses. However, higher doses may not be without risk of toxicity. Growth retardation,¹¹⁻¹⁵ dose-dependent suppression of the HPA,^{6,16} adrenal insufficiency after discontinuation of chronic therapy,^{17,18} and abnormal effects on bone formation,¹⁹ bone turnover,²⁰ and bone density²¹ have recently been reported.

It is likely that higher doses of IGC pose a greater risk for adrenal suppression; unfortunately, the doses

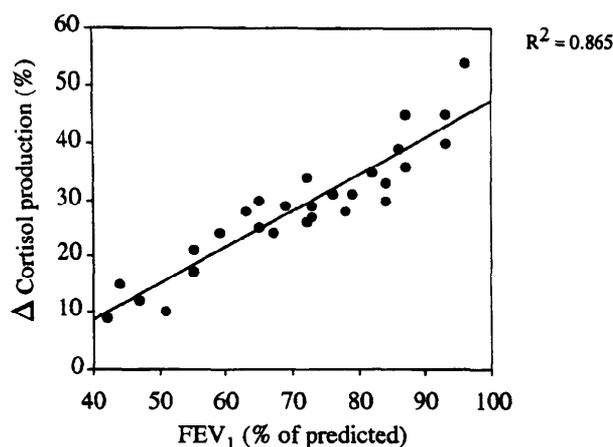


FIGURE 3. The correlation between the FEV₁ just before the inhalation of FP and the fall in cortisol production.

at which the risk for adrenal suppression outweigh the beneficial effects of the drug are not known.

Systemic bioavailability of inhaled drugs may arise from absorption through the GI tract or the lung. Although buccal absorption of IGC is limited by the small absorptive surface area, a high degree of lipid solubility may enhance buccal absorption. Therefore, mouth rinsing following inhalation may reduce oral bioavailability.^{22,23} IGC absorbed from the intestine undergo an extensive degree of first-pass hepatic metabolism. While beclomethasone dipropionate may be transformed to active metabolites, the first-pass metabolism of the newer IGC, FP and budesonide, is 99% and 89%, respectively,^{24,25} with no known biotransformation to an active metabolite.

On the basis of this data, it can be inferred that the systemic bioavailability of IGC is mainly determined by the absorption across the lung vascular bed. Therefore, lung deposition would be expected to determine the systemic absorption and adverse effects of the drugs. Lung deposition of inhaled drugs depends on the delivery system used,⁸ the dose,^{7,22} and, potentially, the degree of airflow obstruction. Melchor and associates⁸ found that lung deposition of inhaled salbutamol was significantly higher in normal subjects than in patients with airflow obstruction, whatever the delivery system. Mean baseline FEV₁ was about 50% of predicted normal values, and lung deposition of the drug was about 75% of the amount of lung deposition in normal subjects. In other studies,^{26,27} significant airflow obstruction (mean FEV₁ = 56% of predicted normal values) was associated with an approximately 50% difference in peak plasma fenoterol concentration following drug inhalation (1.6 ng/mL vs 3.1 ng/mL).

Although increasing the steroid dose for patients with asthma is presumed to be associated with greater clinical efficacy and with higher incidence of systemic effects, clinically relevant dose-response relationships are difficult to prove. Some studies have shown a shallow dose-response relationship.²⁸⁻³⁰ On the other hand, greater incremental changes in efficacy variables at higher doses of IGC were reported by others.^{2,31} It is suggested, therefore, that the dose of IGC required to achieve optimal asthma control varies among patients, due to variations in tissue sensitivity to IGC, the severity of the underlying disease, and, as a logical assumption from the present study (at least for FP), its relation to the degree of airflow obstruction.

The clinical significance of our short-term observation of the effect of FP on the HPA is unclear and should be elucidated in long-term studies. The correlation of such an observation with the systemic side effects of IGC is not clear. Other IGC should also be investigated. In addition, it should be noted

that although our data may not represent total cortisol secretion, it may represent a delay in the peak cortisol secretion because we measured only overnight cortisol secretion until 6:00 AM. Because peak cortisol secretion occurs between 4:00 AM and 8:00 AM, optimally, the study should have continued until 9:00 AM or been conducted over an entire 24-h period.

Guidelines on asthma treatment generally recommend the administration of the lowest dose of IGC compatible with asthma control. It is known in general clinical practice that improved asthma control can be achieved by increasing the dose of IGC. Further studies are needed to quantify lung bioavailability of FP and other IGC in order to allow the clinician to optimize asthma control with the lowest risk for systemic adverse effects.

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LONG-TERM EFFECTS OF BUDESONIDE OR NEDOCROMIL IN CHILDREN WITH ASTHMA

THE CHILDHOOD ASTHMA MANAGEMENT PROGRAM RESEARCH GROUP*

ABSTRACT

Background Antiinflammatory therapies, such as inhaled corticosteroids or nedocromil, are recommended for children with asthma, although there is limited information on their long-term use.

Methods We randomly assigned 1041 children from 5 through 12 years of age with mild-to-moderate asthma to receive 200 μ g of budesonide (311 children), 8 mg of nedocromil (312 children), or placebo (418 children) twice daily. We treated the participants for four to six years. All children used albuterol for asthma symptoms.

Results There was no significant difference between either treatment and placebo in the primary outcome, the degree of change in the forced expiratory volume in one second (FEV_1 , expressed as a percentage of the predicted value) after the administration of a bronchodilator. As compared with the children assigned to placebo, the children assigned to receive budesonide had a significantly smaller decline in the ratio of FEV_1 to forced vital capacity (FVC, expressed as a percentage) before the administration of a bronchodilator (decline in $FEV_1:FVC$, 0.2 percent vs. 1.8 percent). The children given budesonide also had lower airway responsiveness to methacholine, fewer hospitalizations (2.5 vs. 4.4 per 100 person-years), fewer urgent visits to a caregiver (12 vs. 22 per 100 person-years), greater reduction in the need for albuterol for symptoms, fewer courses of prednisone, and a smaller percentage of days on which additional asthma medications were needed. As compared with placebo, nedocromil significantly reduced urgent care visits (16 vs. 22 per 100 person-years) and courses of prednisone. The mean increase in height in the budesonide group was 1.1 cm less than in the placebo group (22.7 vs. 23.8 cm, $P=0.005$); this difference was evident mostly within the first year. The height increase was similar in the nedocromil and placebo groups.

Conclusions In children with mild-to-moderate asthma, neither budesonide nor nedocromil is better than placebo in terms of lung function, but inhaled budesonide improves airway responsiveness and provides better control of asthma than placebo or nedocromil. The side effects of budesonide are limited to a small, transient reduction in growth velocity. (N Engl J Med 2000;343:1054-63.)

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ASTHMA is a disease of chronic airway inflammation characterized by reversible airway obstruction and increased airway responsiveness.¹⁻³ Recent studies have demonstrated that asthma can be associated with impaired lung growth during childhood and with a progressive decline in pulmonary function in adulthood.⁴⁻¹¹ Clinical practice guidelines recommend antiinflammatory medication for the long-term control of persistent asthma; treatment with inhaled corticosteroids or nedocromil is recommended for children.^{1,2}

The Childhood Asthma Management Program was designed to evaluate whether continuous, long-term treatment (over a period of four to six years) with either an inhaled corticosteroid (budesonide) or an inhaled noncorticosteroid drug (nedocromil) safely produces an improvement in lung growth as compared with treatment for symptoms only (with albuterol and, if necessary, prednisone, administered as needed).¹² The primary outcome in the study was lung growth, as assessed by the change in forced expiratory volume in one second (FEV_1 , expressed as a percentage of the predicted value) after the administration of a bronchodilator. Secondary outcomes included the degree of airway responsiveness, morbidity, physical growth, and psychological development.

METHODS

The design and methods of the research program have been described previously.^{7,12-15}

Screening and Schedule of Visits

Between December 1993 and September 1995, we enrolled 1041 children from 5 through 12 years of age at eight clinical cen-

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ters. The children had mild-to-moderate asthma, as defined by the presence of symptoms or by the use of an inhaled bronchodilator at least twice weekly or the use of daily medication for asthma. The children's airway responsiveness to methacholine, as indicated by the concentration of the drug that caused a 20 percent decrease in the FEV₁, was 12.5 mg per milliliter or less. They had no other clinically significant conditions.¹² The children's parents or guardians signed an informed-consent form approved by the local institutional review board. Follow-up visits occurred two and four months after randomization and at four-month intervals thereafter. From March through June 1999 (the end of the treatment period), the children discontinued the study medication and returned two to four months later for spirometry and methacholine challenge. Children who had been using additional medications because of inadequate control of asthma continued to use those medications.

Treatment

Three hundred eleven children were randomly assigned to receive budesonide (Pulmicort, AstraZeneca, Westborough, Mass.) (200 µg twice daily, delivered by two 100-µg actuations of a breath-actuated metered-dose inhaler [Turbuhaler, AstraZeneca]), and 208 were assigned to receive a matching placebo. Three hundred twelve children were assigned to receive nedocromil sodium (8 mg twice daily, delivered by four 2-mg actuations of a pressurized metered-dose inhaler [Tilade, Rhone-Poulenc Rorer, Collegeville, Pa.]), and 210 were assigned to receive a matching placebo. Assignments were made by permuted-blocks randomization with stratification according to clinic.¹⁶ The total daily doses of budesonide (400 µg) and nedocromil (16 mg) were administered as two equal daily doses to maximize adherence to the treatment regimen,¹⁷⁻²⁰ and adherence was also promoted by an educational program.¹⁵ Albuterol (Ventolin, Glaxo Wellcome, Research Triangle Park, N.C.), delivered by two 90-µg actuations of a pressurized metered-dose inhaler, was used as needed for symptoms of asthma or to prevent exercise-induced bronchospasm.¹² A written action plan guided rescue treatment.^{12,15} Short courses of oral prednisone were prescribed for exacerbations of asthma.¹² The addition of beclomethasone dipropionate (168 µg twice daily; Vanceril, Schering-Plough, Kenilworth, N.J.) to the study medication was allowed if the control of asthma was inadequate. If control remained unsatisfactory, replacement or addition of medications was allowed. To account for remission, it was permissible to taper the study medication to a dose of zero (by stepwise reductions from 100 percent to 50 percent to zero), according to defined procedures.¹² Algorithms guided the resumption of the full dose of the study medication.¹²

Outcome Measures

Spirometry was performed twice yearly, with measurements obtained both before and after the administration of a bronchodilator.^{7,12} A methacholine challenge was performed annually.¹² Methacholine challenge was not performed within 28 days of an upper respiratory tract infection or the use of prednisone for exacerbations of asthma.

The children (or their parents or guardians) completed a diary card each day that recorded night awakenings due to asthma, morning and evening peak flows as measured by a peak-flow meter (Assess, HealthScan Products, Cedar Grove, N.J.), use of study medication, use of albuterol for symptoms and to prevent exercise-induced bronchospasm, use of prednisone, absences from school due to asthma, visits to a physician's office or hospital because of asthma, and severity of symptoms.¹²

The children's height (measured by Harpenden stadiometer) and weight were recorded at every visit; the total bone mineral density of the spine from L1 to L4 and the Tanner stage of sexual development (assessed on the basis of the development of pubic hair, genitals [in boys] or breasts [in girls], and testicular volume, each scored from 1 [preadolescent characteristics] to 5 [adult characteristics]) were assessed annually.¹² Skeletal maturation (bone age) during the last eight months of follow-up was determined at a

central reading center by evaluation of a radiograph of the left wrist and hand by the method of Greulich and Pyle²¹ and was used to estimate the projected final height.²² Psychological development was assessed with four neurocognitive tests administered at base line and three years later, and by eight psychosocial questionnaires completed at base line and during annual visits.¹² Psychosocial questionnaires included the Children's Depression Inventory,²³ a 27-item questionnaire completed by the child with regard to the symptoms of depression. The total score for this scale ranges from 0 to 54, with higher scores indicating greater depression. Skin-prick testing, with a core battery of 10 allergens and several locally relevant allergens, was performed at base line and four years later.^{12,14}

Anterior and posterior images of the lens of the eye, taken with a digital retroluminescent camera (Neitz Cataract Screener CT-S, Neitz Instruments, Tokyo) during the last eight months of follow-up, were examined for posterior subcapsular cataracts at a central reading center.²⁴

Statistical Analysis

Our study had 90 percent power to detect a difference of 3.5 percent between either treatment group and the placebo group in the mean change in the FEV₁, expressed as a percentage of the predicted value, after the administration of a bronchodilator, after four to six years of treatment.¹² Data from the two placebo groups were pooled after we determined that the children in the two groups were similar with respect to base-line characteristics and outcomes. Each participant was included in his or her assigned study group, regardless of any adjustments of treatment (intention-to-treat analysis). The degree of change in an outcome measure was determined by subtracting the base-line measurement from the measurement obtained at the last follow-up visit during the treatment period. The difference between each treatment group and the placebo group in each measure of change was determined with use of multiple regression,²⁵ with the change in the measure as the response variable, two indicator variables for the treatment groups, and the following eight covariates: the base-line value of the outcome measure, the child's age at randomization, race (two indicator variables), sex, clinic (seven indicator variables), duration of asthma at base line, severity of asthma at base line, and skin-test reactivity at base line (any reactivity vs. none). The adjusted mean change in each outcome measure in each study group was computed from the regression model by the use of mean values for all covariates.²⁶ Kaplan-Meier estimates of cumulative probability and log-rank tests²⁷ were used to evaluate the time to the first course of prednisone and the time to the initiation of therapy with beclomethasone or any other nonassigned medication for asthma in each treatment group. All analyses were performed with SAS software (version 6.12, SAS Institute, Cary, N.C.). The P values presented are two-sided and have not been adjusted for multiple comparisons. Interim monitoring of results by a data and safety monitoring board took place semiannually; statistical guidelines for stopping the study were not used. In the comparisons among the study groups we used regression models to adjust for small imbalances in base-line measures; however, unadjusted analyses for all outcome measures yielded qualitatively similar results.

RESULTS

Study Population

The three study groups were similar at base line, except for a slightly higher proportion of boys in the nedocromil group (Table 1). The duration of follow-up was similar in all the study groups, with a mean of 4.3 years (Table 2).

Measures of Pulmonary Function

Budesonide treatment improved the FEV₁ after the administration of a bronchodilator from a mean of

TABLE 1. CHARACTERISTICS OF THE PATIENTS AT BASE LINE.*

CHARACTERISTIC	BUDESONIDE (N=311)	NEDOCROMIL (N=312)	PLACEBO (N=418)
Age — yr	9.0±2.1	8.8±2.1	9.0±2.2
Race or ethnic group — no. (%)			
Non-Hispanic white	201 (64.6)	218 (69.9)	292 (69.9)
Non-Hispanic black	44 (14.1)	38 (12.2)	56 (13.4)
Hispanic	32 (10.3)	29 (9.3)	37 (8.9)
Other	34 (10.9)	27 (8.7)	33 (7.9)
Sex — no. (%)‡			
Female	130 (41.8)	106 (34.0)	184 (44.0)
Male	181 (58.2)	206 (66.0)	234 (56.0)
Age at onset of asthma — yr	3.1±2.3	3.1±2.4	3.0±2.6
Time since diagnosis of asthma — yr	5.2±2.6	5.0±2.7	4.9±2.7
Treatments in 6 mo before enrollment — no. of patients (%)			
Cromolyn or nedocromil	133 (42.8)	148 (47.4)	160 (38.3)
Inhaled corticosteroid	126 (40.5)	114 (36.5)	150 (35.9)
Oral corticosteroid	107 (34.4)	94 (30.1)	162 (38.8)
Severity of asthma — no. (%)			
Moderate	166 (53.4)	161 (51.6)	216 (51.7)
Mild	145 (46.6)	151 (48.4)	202 (48.3)
Hospitalizations for asthma in year before enrollment — no./100 person-yr	31	29	31
Recordings on daily diary card			
Episode-free days — no./mo§	9.7±7.8	9.9±8.1	9.6±7.6
Use of albuterol for symptoms — puffs/wk	10.4±9.8	10.5±9.8	10.2±9.6
Night awakenings — no./mo	0.9±1.7	1.0±1.7	0.8±1.5
FEV ₁ before bronchodilator use — % of predicted	93.6±14.4	93.4±14.5	94.2±14.0
FEV ₁ after bronchodilator use — % of predicted	103.2±13.2	102.3±12.7	103.3±12.2
Airway responsiveness to methacholine (FEV ₁ PC ₂₀) — mg/ml¶	1.1±3.3	1.2±3.3	1.1±3.3
Height — percentile	56.8±28.0	56.0±28.7	55.3±28.8

*Plus-minus values are means ±SD. Not all percentages add to 100, because of rounding or because some children used more than one treatment before enrollment.

†FEV₁ denotes the forced expiratory volume in one second, and FEV₁ PC₂₀ the concentration of methacholine that caused a 20 percent decrease in FEV₁.

‡P value for homogeneity among groups = 0.02.

§An episode-free day was defined as a day with no night awakenings, morning and evening peak flow ≥80 percent of personal best peak flow (determined by algorithm¹²), no use of albuterol for symptoms, no use of prednisone, no absence from school or contact with a physician because of asthma symptoms, and no episode of wheezing, coughing, chest tightness, or shortness of breath.

¶Values are geometric means ±SD.

103.2 percent of the predicted value to a mean of 106.8 percent within two months, but this measurement gradually diminished to 103.8 percent by the end of the treatment period, at which point the change in the FEV₁ after bronchodilator use in the budesonide group was not significantly different from that in the placebo group (Table 3 and Fig. 1). The nedocromil group was similar to the placebo group in this measure throughout the treatment period (Table 3 and Fig. 1). The ratio of the FEV₁ to the forced vital capacity (FVC, expressed as a percentage of the predicted value) after bronchodilator use was smaller at the end of the treatment period than at the start in all study groups; the decline in the budesonide group was less than that in the placebo group (1.0 percent vs. 1.7 percent, P=0.08) (Table 3 and Fig. 1).

In patients treated with budesonide, FEV₁ before

the administration of a bronchodilator increased within two months and was significantly higher at the end of the treatment period than it was in those receiving placebo (P=0.02); the nedocromil group was similar to the placebo group with respect to this measure throughout the treatment period (Table 3 and Fig. 1). The FVC (expressed as a percentage of the predicted value) before bronchodilator use increased in all study groups. The increase in the nedocromil group was less than that in the placebo group (P=0.02), whereas the increase in the budesonide group was similar to that in the placebo group (Table 3). The FEV₁:FVC ratio before bronchodilator use was smaller at the end of the treatment period than at the start in all three groups; the decline in the budesonide group was less than that in the placebo group (0.2 percent vs. 1.8 percent, P=0.001) (Table 3 and Fig. 1).

TABLE 2. FOLLOW-UP, ASTHMA TREATMENT, AND MORBIDITY DURING THE TRIAL.*

EVENT	BUDESONIDE (N=311)	NEDOCROMIL (N=312)	PLACEBO (N=418)	P VALUE	
				BUDESONIDE VS. PLACEBO	NEDOCROMIL VS. PLACEBO
Follow-up					
Duration of follow-up (yr)	4.3±0.8	4.3±0.7	4.3±0.7	0.35	0.40
Percentage of scheduled visits completed	95.2	95.2	95.1	0.94	0.92
Percentage of days with completed diary card	85.7	85.6	85.7	0.94	0.65
Percentage of patients in whom primary outcome was measured	98.4	98.4	98.3	0.94	0.94
Asthma treatment					
Percentage of days during which treatment was prescribed					
Budesonide, nedocromil, or placebo only					
Full dose	88.9	78.6	78.4	<0.001	0.89
Tapered to half dose	3.4	3.3	2.3	0.05	0.03
Tapered to zero dose	1.1	1.0	0.6	0.10	0.16
Beclomethasone or other asthma medications	6.6	17.1	18.7	<0.001	0.53
Percentage of days child reported to take prescribed dose of study medication†	73.7	70.2	76.2	0.34	0.01
Prednisone course (no./100 person-yr)‡	70	102	122	<0.001	0.01
Morbidity					
Urgent care visits due to asthma (no./100 person-yr)‡	12	16	22	<0.001	0.02
Hospitalizations due to asthma (no./100 person-yr)‡	2.5	4.3	4.4	0.04	0.99
Fractures (no./100 person-yr)‡	5.7	4.1	5.1	0.59	0.23
No. of eyes with posterior subcapsular cataracts§	0‡	0	0	1.00	1.00

*Plus-minus values are means ±SD. The primary outcome was the forced expiratory volume in one second after bronchodilator use, expressed as a percentage of the predicted value.

†Results are based on daily diaries.

‡Rates have been adjusted for age at randomization, race or ethnic group, sex, clinic, duration of asthma at base line, severity of asthma at base line, and skin-test reactivity at base line.

§Results are based on photographic evaluations of 1909 eyes in 955 children. In one child in the budesonide group, an area in the right eye was classified as a questionable posterior subcapsular cataract on photographic evaluation; the child was found to have a barely measurable (<0.5 mm) posterior subcapsular cataract on slit-lamp examination five months later. Uncorrected Snellen visual acuity in the eye was 20/25. This child received budesonide as study medication, beclomethasone (for a total of 13 months), and oral prednisone (for a total of 38 days) during the trial, as well as an intranasal corticosteroid.

Airway responsiveness to methacholine, expressed as the concentration that caused a 20 percent decrease in FEV₁, improved throughout the treatment period in all three groups (Fig. 1), with the greatest improvement occurring in the budesonide group. At the end of the treatment period, airway responsiveness to methacholine was significantly improved in the budesonide group as compared with the placebo group ($P<0.001$), whereas the change in the nedocromil group was similar to that in the placebo group (Table 3 and Fig. 1).

Health Outcomes

As compared with the placebo group, the budesonide group had a 43 percent lower rate of hospitalization ($P=0.04$), a 45 percent lower rate of visits for urgent care ($P<0.001$), and a 43 percent lower rate of use of courses of prednisone ($P<0.001$) over the treatment period (Table 2). The nedocromil group had a 27 percent lower rate of urgent care visits ($P=$

0.02) and a 16 percent lower rate of use of courses of prednisone ($P=0.01$) than the placebo group, but there was no significant difference in the rate of hospitalization. One death from asthma occurred in the nedocromil group; the child had been receiving supplemental treatment, including inhaled corticosteroids, for several months before her death. One child in the placebo group required intubation for an exacerbation of asthma.

Control of asthma was best in the budesonide group, as indicated by significantly fewer symptoms ($P=0.005$), less use of albuterol for symptoms ($P<0.001$), and more episode-free days ($P=0.01$) (Table 3). Changes in morning peak flow and the number of night awakenings per month were similar in all groups (Table 3). The times to the first course of prednisone and to the initiation of treatment with beclomethasone or other nonassigned asthma medications were significantly longer in the budesonide group than in the placebo group ($P<0.001$) (Fig. 2).

TABLE 3. SPIROMETRIC MEASURES, AIRWAY RESPONSIVENESS, PHYSICAL GROWTH, PSYCHOLOGICAL DEVELOPMENT, AND DIARY-CARD MEASURES ACCORDING TO TREATMENT GROUP.

MEASURE*	MEAN VALUE†			SD‡	P VALUE	
	BUDESONIDE (N=311)	NEDOCROMIL (N=312)	PLACEBO (N=418)		BUDESONIDE VS. PLACEBO	NEDOCROMIL † VS. PLACEBO
Changes in spirometric values after broncho- dilator use						
FEV ₁ (% of predicted)	0.6	-0.5	-0.1	9.6	0.36	0.56
FEV ₁ (liters)	1.04	1.06	1.08	0.40	0.30	0.58
FVC (% of predicted)	0.7	-0.1	0.9	9.3	0.74	0.16
FVC (liters)	1.27	1.29	1.33	0.45	0.05	0.25
FEV ₁ :FVC (%)	-1.0	-1.3	-1.7	5.2	0.08	0.26
Changes in spirometric values before broncho- dilator use						
FEV ₁ (% of predicted)	2.9	0.4	0.9	11.2	0.02	0.57
FEV ₁ (liters)	1.02	0.99	1.01	0.43	0.76	0.58
FVC (% of predicted)	2.3	0.6	2.4	10.0	0.89	0.02
FVC (liters)	1.29	1.28	1.35	0.47	0.07	0.06
FEV ₁ :FVC (%)	-0.2	-1.0	-1.8	6.5	0.001	0.10
Airway responsiveness to methacholine (ratio of follow-up to base-line values)	3.0	1.8	1.9	3.3	<0.001	0.97
Change in height (cm)	22.7	23.7	23.8	5.4	0.005	0.65
Height percentile at last follow-up	51.3	55.2	55.7	15.5	<0.001	0.62
Bone age at last follow-up (yr)	13.7	13.6	13.7	2.5	0.84	0.61
Difference between bone age and chronologic age (yr)	0.2	0.4	0.4	1.1	0.18	0.83
Projected final height (cm)§	174.8	174.8	174.8	4.4	0.86	0.87
Tanner genital stage at last follow-up (boys)¶	3.0	2.8	2.9	0.9	0.53	0.10
Tanner breast stage at last follow-up (girls)¶	3.3	3.2	3.4	0.8	0.56	0.17
Change in bone density (g/cm ²)	0.17	0.17	0.18	0.08	0.53	0.15
Change in total score on Children's Depression Inventory	-3.2	-1.8	-2.2	5.1	0.01	0.35
Changes in daily diary-card measures						
Symptom score	-0.44	-0.38	-0.37	0.37	0.005	0.80
Morning peak flow (liters/min)	131	131	132	67	0.86	0.82
Episode-free days (no./mo)	11.3	9.3	9.3	10.2	0.01	0.97
Use of albuterol for symptoms (puffs/wk)	-7.4	-5.7	-5.3	7.1	<0.001	0.42
Night awakenings (no./mo)	-0.7	-0.6	-0.6	1.1	0.14	0.48

*Changes were calculated by subtracting the base-line values from the values at the last follow-up. FEV₁ denotes forced expiratory volume in one second, and FVC forced vital capacity. The primary outcome measure was the FEV₁ after bronchodilator use, expressed as a percentage of the predicted value.

†Means have been adjusted for the average base-line values of the outcome measure, age at randomization, race or ethnic group, sex, clinic, duration of asthma at base line, severity of asthma at base line, and skin-test reactivity at base line. Only measures with both base-line and follow-up values are included in this table.

‡SD is the standard deviation estimated from the regression model.

§Projected final height was calculated from the prediction equations of Tanner et al.,²² which use height, chronologic age, bone age, and (for girls) age at first menses.

¶The Tanner stage is an assessment of sexual development. The possible scores for genital stage and for breast stage range from 1 to 5, where 1 indicates preadolescent characteristics and 5 indicates adult characteristics.

||The Children's Depression Inventory²³ is a 27-item questionnaire completed by the child with regard to the symptoms of depression. The total score ranges from 0 to 54, where higher scores indicate greater depression.

During the treatment period, the percentage of days on which beclomethasone or another asthma medication was prescribed in addition to or instead of the originally assigned treatment was significantly lower ($P<0.001$) for children assigned to budesonide (6.6 percent) than for those assigned to placebo (18.7 percent); there was no significant difference in the measure between the nedocromil group (17.1 percent) and

the placebo group (Table 2). Compliance with treatment, defined as the percentage of days on which a child was reported to have taken the prescribed dose of study medication, was similar in children assigned to budesonide and those assigned to placebo (73.7 percent and 76.2 percent, respectively), but it was lower in children assigned to nedocromil (70.2 percent) ($P=0.01$ for the comparison with placebo) (Table 2).

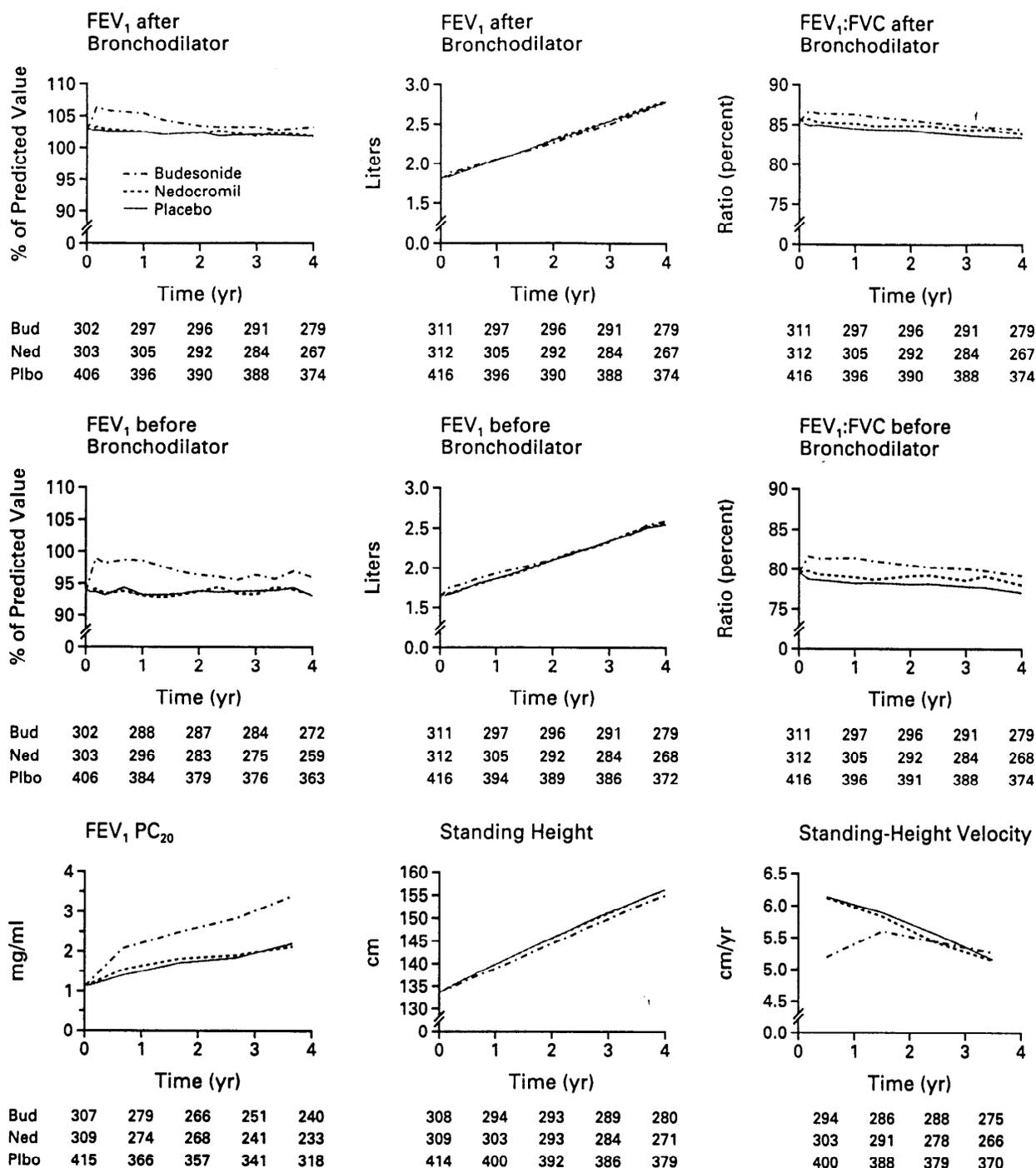


Figure 1. Mean Values for Spirometric Measures before and after the Use of a Bronchodilator, Airway Responsiveness, Standing Height, and Standing-Height Velocity during Four Years of Follow-up in the Budesonide (Bud), Nedocromil (Ned), and Placebo (Plbo) Groups.

The numbers of observations used to calculate means at annual intervals are shown below each panel. When comparisons were made over the total follow-up time, the budesonide group differed significantly ($P < 0.001$) from the placebo group in all measures, even though these differences may not be apparent in every panel, and there were no significant differences between the nedocromil group and the placebo group in any measure. FEV₁ denotes forced expiratory volume in one second, FVC forced vital capacity, and FEV₁ PC₂₀ airway responsiveness measured by the concentration of methacholine that caused a 20 percent decrease in FEV₁. For FEV₁ PC₂₀, values were obtained at 0, 8, 20, 32, and 44 months. P values for the comparisons between study groups of the changes from base line to last follow-up are shown in Table 3.

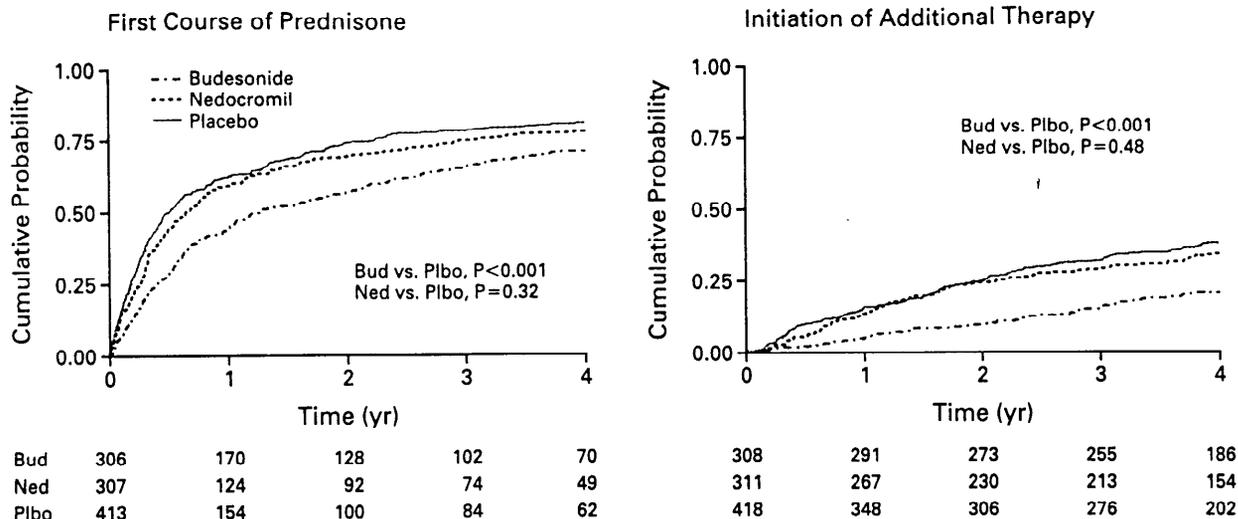


Figure 2. Kaplan-Meier Estimates of the Cumulative Probability of a First Course of Prednisone and Initiation of Additional Therapy (Beclomethasone or Other Nonassigned Asthma Medications) during Four Years of Follow-up in the Budesonide (Bud), Nedocromil (Ned), and Placebo (Plbo) Groups.

The numbers of children at risk at annual intervals are shown below each graph.

Measures of Growth and Assessment for Cataracts

At the end of the treatment period, the mean increase in height in the budesonide group was 1.1 cm less than the mean increase in the placebo group (22.7 vs. 23.8 cm, $P=0.005$); the height increase was similar in the nedocromil and the placebo groups (Table 3). The difference between the budesonide and placebo groups in the rate of growth was evident primarily within the first year of treatment and did not increase later: all groups had similar growth velocity by the end of the treatment period (Fig. 1), as well as similar changes in bone density (Table 3). At the end of treatment, the bone age, projected final height, and Tanner stage in the budesonide and nedocromil groups were similar to those in the placebo group (Table 3). The only difference with respect to changes in any of the psychosocial measures was a greater improvement in the total score on the Children's Depression Inventory,²³ indicating less depression, in the budesonide group as compared with the placebo group (a decline of 3.2 vs. 2.2, $P=0.01$) (Table 3). None of the children had posterior subcapsular cataracts according to lens-photography criteria (Table 2). However, one child in the budesonide group was classified as having a questionable posterior subcapsular cataract. A barely measurable (<0.5 mm) posterior subcapsular cataract was found in this child on slit-lamp examination by an ophthalmologist five months after the photographs were taken. The uncorrected Snellen visual acuity in the eye was 20/25. This child received budesonide as study medication, beclomethasone (for 13 months), and oral prednisone (for 38

days) during the study, as well as an intranasal corticosteroid.

Discontinuation of Study Medication

Four months after discontinuation of the study medication, the children assigned to nedocromil had a smaller reduction from base line in the FEV₁:FVC ratio after bronchodilator use than did those assigned to placebo (a decline of 1.2 percent vs. 2.2 percent, $P=0.03$). Also at this time, children assigned to budesonide or nedocromil had a smaller reduction in FEV₁:FVC before bronchodilator use than did those assigned to placebo (budesonide vs. placebo: a decline of 0.9 percent vs. 2.5 percent, $P=0.005$; nedocromil vs. placebo: a decline of 1.1 percent vs. 2.5 percent, $P=0.01$). The groups were similar in all other measures, including airway responsiveness, which worsened in the budesonide group during the four-month period after discontinuation of budesonide and became similar to that in the placebo group (data are available elsewhere*).

DISCUSSION

The finding that neither budesonide nor nedocromil improved lung function, as measured by the percentage of the predicted value for FEV₁ after the administration of a bronchodilator, was unexpected. FEV₁ was chosen as the primary outcome measure because it is widely accepted as the most clinically

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useful and predictive measure of lung function. It is highly reproducible and correlates well with the progression of disease,^{28,29} use of health care,³⁰ and severity of asthma^{1-3,31} and accurately describes the natural history of childhood asthma. The value after bronchodilator use was chosen as the outcome measure because it minimizes the effects of airway constriction and has less variability over time in individual patients than the value before bronchodilator use.

The use of budesonide was associated with improvement in the FEV₁ before bronchodilator use, when measured as a percentage of the predicted value, but not when measured in liters (Table 3). The use of nedocromil was not associated with improvement in either measure of FEV₁. Since predicted values depend on height,^{32,33} the statistical significance of the change in the FEV₁ as a percentage of the predicted value is mostly attributable to the slightly smaller stature of the children in the budesonide group.

As a consequence of normal lung growth,³⁴ the FEV₁:FVC ratio before bronchodilator use decreased over time in all three groups (Fig. 1). The decrease was minimized by budesonide (before bronchodilator use, $P=0.001$; after bronchodilator use, $P=0.08$). The minimization of the decrease was not due to improvement in FEV₁ and might have been due to lower FVC or improved bronchodilation in the budesonide group.

During the trial, there was a lack of decline in the FEV₁ before and after bronchodilator use in the placebo group and a lack of long-term improvement in the budesonide and nedocromil groups as compared with the placebo group. An irreversible deterioration in lung function might have occurred in the patients before their enrollment, and the treatment might therefore have been too late to effect a change. Eighty percent of all childhood asthma is diagnosed by the age of six years,³⁵ and normal proliferation of the alveoli and airway development occur predominantly before the age of five years.³⁶ We enrolled children from 5 through 12 years of age, who had had asthma for a mean of five years. Some studies recommend initiating treatment within two to three years after the onset of disease.⁹

In contrast to the results of lung-function measurements, our findings on airway responsiveness and health outcomes clearly favor budesonide. As expected,³⁷ improvement in airway responsiveness to methacholine occurred during the treatment period in all three study groups (Fig. 1) but was substantially and significantly greater in the budesonide group (Table 3); this finding is consistent with the results of shorter trials in children.^{38,39} The relative improvement in the budesonide group suggests additional improvement as a consequence of lower bronchomotor tone or diminished airway inflammation.

The rates of hospitalization and of urgent care visits and the need for additional therapy and oral prednisone were lowest in the budesonide group (Table 2).

Budesonide was also associated with a greater reduction in symptoms and in the use of albuterol for symptoms and with an increase in the number of episode-free days as compared with placebo (Table 3).

We also evaluated the long-term effects of inhaled nedocromil in children. Overall, the results in the nedocromil group were similar to those in the placebo group, except that nedocromil was associated with fewer exacerbations, as evidenced by a lower rate of prednisone use and a lower rate of urgent care visits.

The current literature indicates that treatment of children with inhaled or nasal corticosteroids, specifically beclomethasone dipropionate, results in a loss of 0.7 to 1.4 cm in linear growth over a one-year period.³⁸⁻⁴⁶ Our four-to-six-year trial provides evidence that the effect of budesonide on growth velocity is not sustained and that extrapolations from one-year studies to projected loss in subsequent years are not appropriate. Calculations of projected final height²² suggest that the children in the study groups will achieve similar final heights.

There were no significant differences among the three groups in the change in bone density. Several recent studies have suggested that the use of high doses of inhaled corticosteroids in adults can lead to the development of cataracts.^{47,48} In one child in the budesonide group, an area of one eye was classified as a questionable posterior subcapsular cataract on photographic assessment. However, interpretation of this finding was complicated by the child's use of oral corticosteroids and the lack of base-line photographic assessment.

After discontinuation of the study medication, no differences were observed among the study groups in lung function or growth from base line (the beginning of the study) to the final measurement, except for the FEV₁:FVC ratio before bronchodilator use. The increase in responsiveness to methacholine seen in the budesonide group after discontinuation of the study medication suggests that the beneficial effect of budesonide on airway responsiveness to methacholine is due to changes in bronchomotor tone or airway inflammation, and not to the prevention or resolution of remodeling of the airway wall.

The percentage of days on which only the full dose of the assigned study medication was prescribed was greater in the budesonide group than in the placebo group (88.9 percent vs. 78.4 percent, $P<0.001$) (Table 2). However, it is unlikely that this difference substantially influenced the findings. Four post hoc analyses confirmed the results of the intention-to-treat analysis. These analyses excluded any outcome measures obtained after departure from full-dose study medication, were restricted to children who used only full-dose study medication throughout the follow-up, included only children who had reported compliance with full-dose study medication on at least 80 percent of days, and categorized children according to their

prescribed treatment at the end of the treatment period (data are available elsewhere*).

Our study demonstrates the importance of long-term, controlled trials of treatment for asthma. A benefit of budesonide in terms of lung function, as measured by the FEV₁ after bronchodilator use, was evident at one year, but not at four years; a reduction in linear growth velocity in children treated with budesonide was evident at one year but was absent by the second year. Airway responsiveness to methacholine improved in all study groups over the four to six years of treatment. The improvement was substantially and significantly greater with budesonide than with placebo, but this advantage disappeared after the discontinuation of treatment with budesonide.

In summary, we found that in children five or more years of age with mild-to-moderate asthma, continuous daily treatment with inhaled budesonide or nedocromil had no therapeutic benefit in terms of lung function, as measured by the FEV₁ after bronchodilator use, as compared with therapy given as needed for the control of symptoms (as in the placebo group). Intervention with antiinflammatory medications earlier in childhood, earlier after the onset of disease, or in patients selected because of a decline in pulmonary function might still be beneficial and should be evaluated. Continuous daily treatment with inhaled budesonide leads to better control of asthma than symptomatic treatment (as in our placebo group) or treatment with nedocromil, and its side effects are limited to a small, transient reduction in growth velocity. Inhaled corticosteroids are safe and effective for long-term use in children with asthma.

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Comparison of fluticasone propionate and sodium cromoglycate for the treatment of childhood asthma (an open parallel group study)

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Inhaled corticosteroids are highly effective in the treatment of asthma at all ages and their use in younger children is increasing. As concerns exist about the long-term systemic side-effects of high dose inhaled corticosteroids, current guidelines continue to recommend sodium cromoglycate (SCG) as first line regular medication for children with frequent symptoms. Few published studies have compared the safety and efficacy of inhaled corticosteroids with SCG in children. This study compares SCG with the new inhaled corticosteroid, fluticasone propionate (FP), which has theoretical advantages over other currently available corticosteroids due to its negligible oral bioavailability.

This was a randomized, open, multi-centre, parallel group comparison of 50 µg FP twice daily and 20 mg SCG four times daily over 8 weeks, preceded by a 2-week baseline period. Sixty-two general practices and two hospital centres enrolled 225 asthmatic children aged 4–12 years (110 received FP; 115 received SCG). Outcome measures improved in both groups, with a significant difference in favour of FP for the key variables of mean morning and evening % predicted PEFR and % of symptom-free days and nights. No significant difference was observed for FEV₁, or relief medication use. Two children taking FP and 10 children taking SCG withdrew because of adverse events.

This study showed that low dose FP was effective and superior to SCG in young children with mild–moderate asthma. Safety studies of longer duration are needed before changing the current recommendations for inhaled corticosteroid therapy.

Introduction

Inhaled corticosteroids are highly effective in the treatment of moderate and severe asthma at all ages and their use in younger children is increasing. Effects on function of the hypothalamic–pituitary–adrenal (HPA) axis can be detected when inhaled corticosteroids are given at doses of 400 µg day⁻¹ (or greater) and at the moment there is little information about possible long-term systemic effects in children who start treatment with inhaled corticosteroids in infancy or the pre-school years (1–3). For these reasons, the recently published international consensus on the management of childhood asthma continues to recommend sodium cromoglycate (SCG) as the first line regular medication for children

with frequent symptoms (4). The current recommendations for inhaled corticosteroid therapy are for children who fail to respond to or comply with SCG therapy, or have severe asthma. The efficacy and safety of SCG are well established and this drug will provide good asthma control in about 60% of children with frequent symptoms (5,6). There are few published studies which have compared the safety and efficacy of inhaled corticosteroids with SCG in children (7–13).

Fluticasone propionate (FP) is a new inhaled corticosteroid currently under investigation. Preliminary work indicates it is a strong agonist at the glucocorticoid receptor conferring potent topical activity (14). Oral bioavailability is negligible (<1%) (15). This is attributed to incomplete gastrointestinal absorption and virtually complete hepatic first pass metabolism to the inactive 17-β-carboxylic acid. Although currently available inhaled corticosteroids in doses up to 400 µg day⁻¹ are clinically safe, some children with more severe asthma may require life

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long prophylaxis, perhaps starting in very early childhood. There is the possibility of long-term effects on bone metabolism (16) but FP, with its negligible oral bioavailability and improved safety margin, does have theoretical advantages over the currently available inhaled corticosteroids, particularly in young children. A study of short-term growth, as measured by knemometry, confirmed that FP had a significantly lower systemic effect than the clinically equivalent dose of beclomethasone dipropionate (17). Large multi-centre studies, conducted for regulatory purposes in asthmatic children, have found FP to be superior to placebo (18) and have suggested its clinical potency to be double that of beclomethasone dipropionate (19). The aim of this study was to compare the efficacy and tolerability of inhaled FP with SCG in children who had previously received only intermittent treatment with bronchodilators, and who were receiving regular inhaled medication for the first time.

Methods

TRIAL DESIGN

This was a multi-centre, open, randomized, parallel group study comprising a 2-week baseline period and an 8-week treatment period in which 20 mg SCG four times daily was compared with 50 µg FP twice daily. Asthmatic children aged 4–12 years who had previously received only intermittent bronchodilator therapy and had never been treated with inhaled SCG or an inhaled corticosteroid, but who, on clinical grounds, were being considered for regular treatment, were recruited into the baseline assessment period. The diagnosis of asthma was based on clinical history which included recurrent episodes of wheeze and cough which had responded to bronchodilator therapy. Children who had received oral corticosteroids in the previous 6 weeks or who had been given more than three short courses of systemic corticosteroid therapy in the previous 6 months were not included. Children who had suffered a respiratory tract infection in the preceding 2 weeks were also excluded.

Before commencement of the baseline assessment, forced expiratory volume in 1 s (FEV_1) was recorded by spirometry. Peak expiratory flow rate (PEFR) was measured with a mini-Wright peak-flow meter after inhalation of 400 µg of salbutamol, in order to establish the maximum achievable PEFR. Children were taught to use the mini-Wright peak-flow meter and were only included in the study if they could demonstrate its correct use. Each child was given the appropriate meter according to age and baseline peak-flow (either a standard or low reading meter).

They were asked to record the best of three blows each morning and evening and use the same meter throughout the trial. Current bronchodilator medication was replaced by salbutamol administered by the Rotahaler™ device to be taken as required. Eligibility for the treatment period was determined during the 2-week baseline period. Symptoms of cough, wheeze, disturbance of sleep or daytime activity, morning and evening PEFR and use of relief medication were recorded daily on diary cards at home. Children entered the treatment period if, on at least 7 days of the baseline period, they had reported asthma symptoms requiring one or more doses of inhaled salbutamol, or had recorded morning PEFRs of less than 80% of their maximum.

The children who fulfilled the entry criteria were then randomly allocated to receive either 20 mg SCG four times daily by capsule powder device, or 50 µg FP twice daily by Diskhaler™ device. Randomization was in balanced blocks of six, with each centre allocated at least one block.

The children continued to take 200–400 µg salbutamol by Rotahaler for symptomatic relief. They and their parents continued to make recordings on diary cards at home as in the baseline period. Each child was reviewed after 2 weeks, 5 weeks and on completion of the 8 weeks' treatment. At each visit, the diary card was collected and replaced with a new one. Inhaler techniques were checked.

The oropharynx was examined and swabs taken if clinically indicated. FEV_1 was measured by spirometry. Compliance with treatment was assessed by discussion with parents and from medication records in the patients' diary cards. Adverse events and concomitant illness were documented.

The protocol used was designed by the authors. The study was conducted by the Clinical Research Department of Allen & Hanburys Limited, through the collaboration of their Clinical Research Scientists and the participating physicians. As the intention was to recruit children who had never received regular medication, the trial was almost entirely based in general practices. The results and statistical analysis were independently reviewed by the Department of Applied Statistics at Reading University and by the authors.

The study was approved by the Ethics Committee of each participating centre, and written informed consent to participate in the study was obtained from the parent or legal guardian of each child. The study was conducted in accordance with the Declaration of Helsinki (as revised in Hong Kong, 1989), and with Good Clinical Practice guidelines as issued by the European Community (1990).

STATISTICAL ANALYSIS

The primary variable for comparing the efficacy of treatments was the change (from baseline) in mean morning % predicted PEFR at 0-2, 2-5, and 5-8 weeks' treatment. If the smallest mean difference in change of % predicted PEFR of clinical relevance between the groups is 5%, then assuming a SD common to both groups of 11% of predicted and 5% two-tailed significance, approximately 100 evaluable patients were required in each treatment group for a test at 90% power. PEFR data were expressed as the percentage of the patients' predicted values related to height (20) and were analysed by multi-variate analysis of variance. For the secondary variables, change from baseline FEV₁ (expressed as % predicted) at the end of the treatment period was compared between the treatment groups using the student's *t*-test; the percentage of days and nights on which the children were symptom-free and the frequency of use of relief medication were derived from the diary cards, and *z*-tests, i.e. using the normal distribution, were used to compare treatments at each time point. The student's *t*-test was used to test for differences between the two treatment groups in mean % predicted morning PEFR at baseline. The level of significance for all analyses was taken to be $P < 0.05$. Confidence intervals were calculated at the 95% level.

Results

Three hundred and five asthmatic children were recruited from 62 general practices and 2 hospital centres. Two hundred and twenty-five of them fulfilled the baseline entry criteria and entered the treatment period. One hundred and fifteen received SCG and 110 received FP. Although none had received regular medication, many were experiencing frequent symptoms but there were no obvious demographic differences nor statistically significant differences in asthma severity between the two treatment groups (Table 1).

There was a significant difference in morning PEFR in favour of FP during the treatment period. Multi-variate analysis of variance showed that the treatment difference changed over time, increasing to 7.5% of predicted at 6-8 weeks ($P = 0.0001$). At this time, the 95% confidence interval showed that the true difference in favour of FP was likely to be at least 3.8% and could be as much as 11.2% of predicted. The difference for evening PEFR also favoured FP but only in the latter part of the treatment period, reaching a maximum of 5.6% of predicted during the last 2 weeks. The 95%

Table 1 Baseline patient data

	Fluticasone	Sodium propionate cromoglycate
Number	110	115
Male	64	66
Female	46	49
Age (years) Mean	8.5	7.9
Range	4.1-12.7	4.1-12.9
Proportion of:		
Symptom-free days (median)	0.14	0.15
Symptom-free nights (median)	0.46	0.46
Relief medication:		
Mean doses day ⁻¹ (SD)	1.97 (1.37)	1.91 (1.25)
Mean doses night ⁻¹ (SD)	0.50 (0.53)	0.61 (0.62)
PEFR (mean % predicted)		
Morning (SD)	93.1 (21.6)	89.9 (20.6)
Evening (SD)	97.6 (23.5)	93.1 (21.3)
FEV ₁ (mean % predicted) (SD)	79.1 (16.3)	77.8 (16.7)

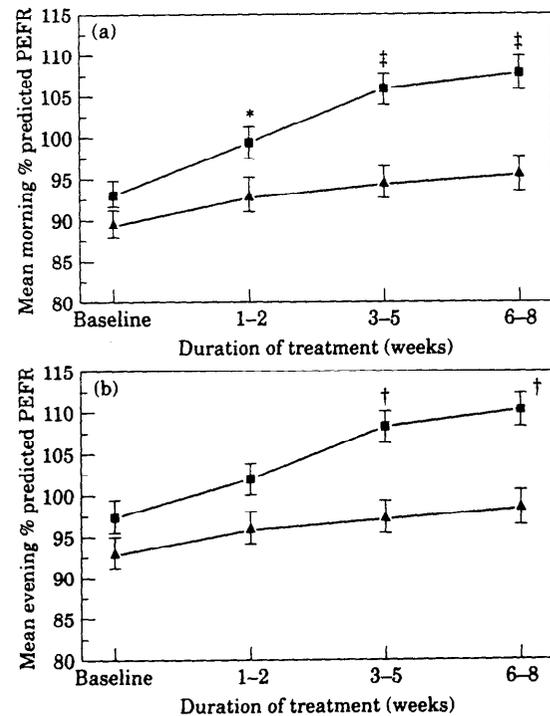


Fig. 1 Mean PEFR (SE) expressed as % of predicted, (a) morning, (b) evening. ■, Fluticasone propionate ($n = 110$); ▲, Sodium cromoglycate ($n = 115$); * $P < 0.05$; † $P < 0.0001$.

confidence interval was 2.3-9.0% of predicted; $P = 0.0011$ at 6-8 weeks (Fig. 1).

In both groups, FEV₁ improved during treatment. With FP, mean % predicted FEV₁ increased from

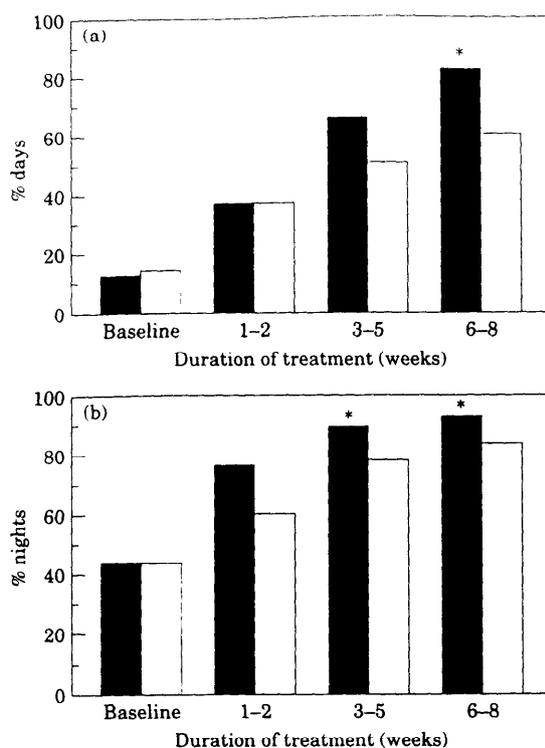


Fig. 2 Median percentage of symptom-free days (a) and nights (b) for each period of assessment during the study. Solid bar, fluticasone propionate; Open bar, sodium cromoglycate; * $P < 0.05$.

79.1 (SD 16.3) to 87.8 (SD 16.6%) of predicted and with SCG, the increase was from 77.8 (SD 16.7) to 82.4 (SD 16.1)% of predicted. There was no evidence of a difference between treatments ($P = 0.27$).

During the 2-week baseline period, the children had frequent symptoms and required bronchodilator treatment on most days. The median percentage of symptom-free days was about 15%, and symptom-free nights about 45%. The percentage of symptom-free days increased markedly on both treatments. The median percentages reached 84% with FP and 62% with SCG in the last 2 weeks. Symptom-free nights increased to 95% with FP and to 84% with SCG. There was a difference in favour of FP for the percentage of symptom-free nights at 3-5 weeks and at 6-8 weeks, and for the percentage of symptom-free days at 6-8 weeks (in all three cases, $P < 0.05$). Point estimates suggest that this difference could represent at least two more symptom-free days and nights with FP than with SCG in the last 3 weeks of the treatment period (Fig. 2). The requirement for relief medication declined in both treatment groups with no obvious difference between the two (Table 2).

Table 2 Relief medication - mean number of doses of salbutamol

	Fluticasone propionate		Sodium cromoglycate	
	Day	Night	Day	Night
Baseline	1.97	0.50	1.91	0.61
Weeks 1-2	0.78	0.20	0.97	0.35
Weeks 3-5	0.60	0.14	0.74	0.28
Weeks 6-8	0.49	0.09	0.64	0.21

Table 3 Adverse events leading to withdrawal from the study

Adverse events	Number of patients	
	Fluticasone propionate (n=110)	Sodium cromoglycate (n=115)
Exacerbation of asthma	1	1
Acute chest pain	1	—
Breathless and wheeze	—	1
Burning sensation in chest	—	1
Sore throat	—	1
Stevens-Johnson syndrome	—	1
Medication-induced coughing	—	1
Medication-induced sickness	—	2
Unacceptable taste of medication	—	2
Total no. of patients who withdrew due to an adverse event	2	10

Of the 225 patients who entered the treatment period, 37 (16%) withdrew, 11 from the FP group and 26 from the SCG group. Twenty-five withdrew for reasons which appeared to be unrelated to the treatment. Two children taking FP and 10 children taking SCG withdrew because of adverse events (Table 3). Hoarse voice and oropharyngeal candidiasis were not observed in any of the children.

Discussion

Treatment with FP was superior to SCG for the primary variable, morning PEF, and for the secondary variables of evening PEF and symptom-free days and nights. The mean difference between treatments of 7.5% of predicted in morning PEF is likely to be of clinical importance in terms of asthma management, as is an increase of 2 symptom-free days per 3 weeks. Additional analysis showed that

the improvement during treatment with SCG was significant (mean morning % predicted PEFR increased 7.8%; 95% CI 5.3–10.2; $P < 0.0001$). However, the study was not placebo-controlled and some or all of the effect could be attributable to the 'clinical trial effect' (21). With a treatment period of 8 weeks, it is possible that neither therapy had reached its maximal effect, but there was no indication from the data that a longer treatment period would have changed the direction of the treatment difference.

For practical reasons, the study was conducted in an open fashion. As the two drug treatments look very different and the frequency of administration varies, the only way to make the study blind would have been to use a double dummy technique. The requirement for the children to take two separate inhaled treatments would probably have affected both recruitment and compliance. The 'clinical trial effect' was likely to have been similar with both treatments since these children had never received regular inhaled medication before, so both would represent a 'new' form of therapy. The primary variable was an objective measure of lung function. The statistical analysis was done by a department who had no clinical involvement with the patients, and assessed by an independent university statistics department.

Compliance with treatment could have influenced the results. It has been shown that compliance with four times a day administration is poorer than compliance with twice daily administration of inhaled therapy. On the basis of recorded medication use in diary cards during treatment, 23 patients (20 SCG:3 FP) were judged to have taken less than 75% and one patient (FP) to have taken more than 125% of their medication. Four other patients (two in each group) failed to record use of medication. When the data for morning and evening PEFR were re-analysed as per-protocol analyses, excluding these 28 patients, there was still strong evidence of a treatment difference in favour of FP. At weeks 6–8, the treatment difference in mean morning PEFR expressed as % predicted was 7.0% points in favour of FP (99% CI 1.1–12.8; $P = 0.0022$). Similarly, for evening PEFR, the treatment difference was 5.6% points in favour of FP (99% CI 1.2–10.0; $P = 0.0011$).

Recruitment to the study was aimed at children with mild–moderate asthma who were being considered for introduction of preventive therapy. No children entering the study had received SCG therapy or an inhaled corticosteroid in the past. It was notable, however, that the mean FEV₁ before entering the trial was less than 80% of predicted and, during the 2 weeks of pre-treatment assessment,

many children were experiencing symptoms which required bronchodilator therapy on most days. This emphasizes the importance of daily evaluation of symptoms, and the use of objective measurement of lung function when deciding on the need for regular treatment.

Only a few small studies have compared SCG and inhaled corticosteroid treatment in childhood asthma. Three clinical trials comparing 4-week treatment periods and involving 40 children aged 7–15 years (7), 20 children aged 6–13 years (8) and 24 children aged 4–26 years (9) found an inhaled corticosteroid (betamethasone valerate or beclomethasone dipropionate) to be superior to SCG in terms of wheeze-free days and peak-flow rates recorded at home. The doses of inhaled corticosteroid used in these studies, ranging from 400–800 $\mu\text{g day}^{-1}$, were much larger than that used in the present trial. The dose of FP given in this study corresponds to beclomethasone 200 $\mu\text{g day}^{-1}$ (22). One trial did not detect any difference in efficacy between SCG and beclomethasone dipropionate but the power to detect a difference was low because numbers were so small (14 subjects aged 5–15 years) (10). Two further studies in children with severe asthma suggested that substitution of an inhaled corticosteroid improves asthma in children who respond inadequately to treatment with SCG (11,12). At the time these studies were done, there was no long-term experience of the use of inhaled corticosteroids in children and their use was largely confined to school-age children with severe asthma. It has since been shown that at these higher doses, it is possible to demonstrate some systemic effect on HPA axis (1–3). In a more recent study, Kraemer *et al.* found a greater improvement in lung mechanics and in non-specific bronchial reactivity in children given 100–200 μg beclomethasone dipropionate three times daily, compared with those given 20 mg SCG three times daily for 8 weeks (13). None of the published studies have addressed the question of the relative speed of action of the drugs. It is interesting that in the present study there was evidence of a difference in treatment effect in favour of FP for morning PEFR during the first 2 weeks of the treatment period (Fig. 1a).

No clinically serious, adverse events were reported with either drug but events resulting in withdrawal from the study were more frequent with SCG than with FP. Most of the adverse events were respiratory and seemed to indicate poor asthma control. Five children complained of retching, vomiting or an unpleasant taste after taking SCG by capsule powder device. The study period was short and no formal

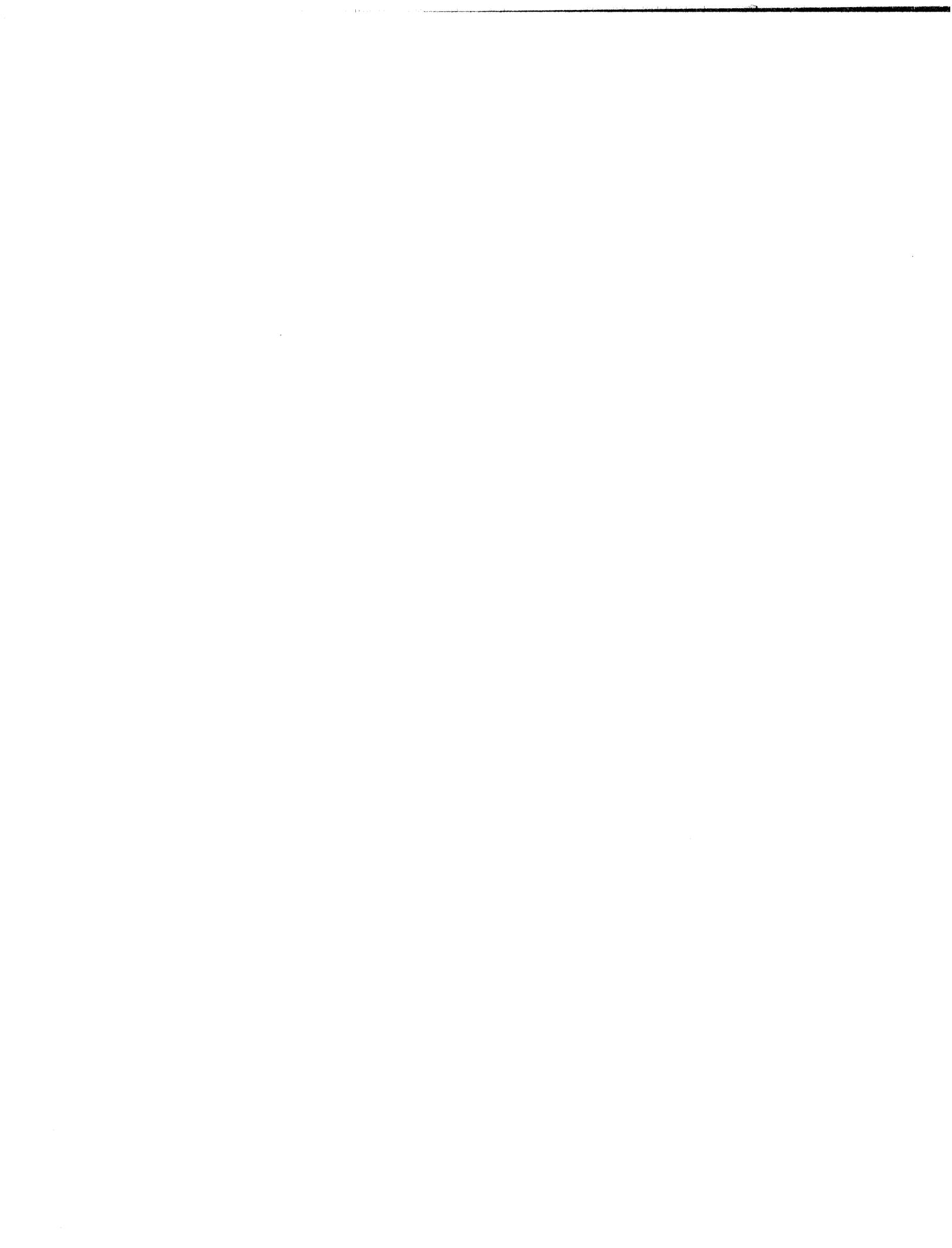
assessment was made of adrenal axis function in the children taking FP. Studies of much longer duration with this new inhaled corticosteroid are needed before considering a change in the current recommendations for regular inhaled corticosteroid therapy in children with mild-moderate asthma. Nevertheless, the favourable results with FP in terms of efficacy and tolerability suggest that, in due course, it may be appropriate to lower the threshold for the administration of this inhaled corticosteroid to children, both in terms of age and severity of symptoms.

Acknowledgements

The authors would like to thank the 62 general practices and 2 hospital centres who undertook this study. They would also like to thank the Allen & Hanburys Clinical Research Department, Glaxo Pharmaceuticals Statistics & Data Management Department and the Applied Statistics Department of Reading University for all their help and support. Rotahaler and Diskhaler are trade marks of the Glaxo Group of Companies.

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EFFECT OF LONG-TERM TREATMENT WITH INHALED BUDESONIDE ON ADULT HEIGHT IN CHILDREN WITH ASTHMA

LONE AGERTOFT, M.D., AND SØREN PEDERSEN, M.D., DR.MED.SCI.

ABSTRACT

Background Short-term studies have shown that inhaled corticosteroids may reduce the growth of children with asthma. However, the effect of long-term treatment on adult height is uncertain.

Methods We conducted a prospective study in children with asthma to examine the effect of long-term treatment with inhaled budesonide on adult height. We report on 211 children who have attained adult height: 142 budesonide-treated children with asthma, 18 control patients with asthma who have never received inhaled corticosteroids, and 51 healthy siblings of patients in the budesonide group, who also served as controls.

Results The children in the budesonide group attained adult height after a mean of 9.2 years of budesonide treatment (range, 3 to 13) at a mean daily dose of 412 μg (range, 110 to 877). The mean cumulative dose of budesonide was 1.35 g (range, 0.41 to 3.99). The mean differences between the measured and target adult heights were +0.3 cm (95 percent confidence interval, -0.6 to +1.2) for the budesonide-treated children, -0.2 cm (95 percent confidence interval, -2.4 to +2.1) for the control children with asthma, and +0.9 cm (95 percent confidence interval, -0.4 to +2.2) for the healthy siblings. The adult height depended significantly ($P < 0.001$) on the child's height before budesonide treatment. Although growth rates were significantly reduced during the first years of budesonide treatment, these changes in growth rate were not significantly associated with adult height.

Conclusions Children with asthma who have received long-term treatment with budesonide attain normal adult height. (N Engl J Med 2000;343:1064-9.)

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BECAUSE they are effective, inhaled corticosteroids are widely used to treat children with asthma.¹⁻³ However, many physicians are concerned about the potential adverse effects of long-term corticosteroid treatment, particularly effects on growth.

In many trials assessing growth during therapy with inhaled corticosteroids, follow-up observations have been conducted for one year or less. Although such studies may provide useful information, their relevance to actual practice is uncertain.⁴ Several studies have reported poor correlations between corticosteroid-induced short-term changes in the growth rate of the lower leg and total body growth during the subsequent year.⁵⁻¹⁰ Furthermore, the correlation be-

tween consecutive annual measurements of statural height velocity in normal prepubertal children is poor, with only partial correlation between values at one, two, three, and four years.⁸ Height velocity computed over periods of three and four years during childhood explains only 34 percent and 38 percent, respectively, of the variation in adult height.⁸

Since 1986, we have been conducting a prospective study of children with persistent asthma to assess total body growth, weight gain, lung function, and hospitalization for asthma exacerbations.^{2,11,12} We report here the 10-year growth data for the children who have reached adult height. We also report how growth rate and changes in growth rate relate to adult height.

METHODS

Study Design

Children with asthma were recruited for a prospective, long-term study.^{2,11,12} We excluded those with other chronic diseases or with a gestational age of less than 32 weeks. All children visited the clinic at six-month intervals for one to two years (the run-in period). During this period, asthma medication was adjusted according to the Danish pediatric asthma guidelines in use at the time.¹³ Three hundred thirty-two children whose asthma was considered to be acceptably controlled without the continuous use of inhaled corticosteroids were then asked to change to treatment with the inhaled corticosteroid budesonide, because several studies had indicated that inhaled corticosteroids should be used more frequently.^{14,15} The proposed change in therapy was accepted by the families of 270 children (the budesonide group). The families of 62 children declined to change therapy because of concern about side effects or satisfaction with their current therapy. These children (the controls) continued to take the medication they had used during the run-in period. Control patients were able to change to inhaled budesonide if they chose to at a later time. The study was approved by the ethics committee of Vejle and Fyns counties, and oral informed consent was obtained from all families.

At each six-month visit, we recorded the number of hospital admissions for acute asthma, age, height (mean of three measurements with a Harpenden stadiometer), weight, lung function (as assessed with a bellows spirometer), the dose and frequency of administration of all prescribed drugs, the dose of inhaled budesonide, and the inhalation device used. Changes in medication, if any, were based on a combination of history, lung function, use of a β_2 -agonist for rescue therapy, and diary recordings. During the first six years of the study, fixed clinical criteria were used to initiate changes in medication.² After this time, the criteria were more flexible.

Throughout the study, the patients were seen by the same two physicians, and all measurements of weight, height (including the heights of siblings and parents), and lung function were performed by the same three nurses. Between scheduled visits, all changes in asthma medication were made under the supervision of the clinic personnel and were recorded. Any asthma medication required to

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EFFECT OF LONG-TERM TREATMENT WITH INHALED BUDESONIDE ON ADULT HEIGHT IN CHILDREN WITH ASTHMA

control the disease was allowed. Data for children who received prednisolone for more than an average of two weeks per year were excluded from the analysis of adult height. Compliance with asthma medication was checked at each visit by direct questioning and by recording the frequency of renewal of prescriptions.

The data analyzed here were collected from January 1986 through August 1999. The status of the 332 originally enrolled patients at the end of this period is shown in Figure 1. Among those who had reached adult height and for whom information on parental height was available, there remained 142 subjects in the budesonide group and 18 in the control group. The mean age at the diagnosis of asthma was 3.4 years (range, 1 to 10) in the budesonide group and 4.3 years (range, 1 to 9) in the control group. Because data on adult height in children who were not using inhaled corticosteroids were limited because of the small number of children remaining in the control group, the healthy siblings of the children in the budesonide group were recruited for measurement of adult height. There were 149 siblings, of whom 105 had reached adult height. Of these, 38 had received treatment with inhaled corticosteroids and

16 refused to participate, leaving 51 healthy siblings for analysis (Table 1).

Statistical Analysis

Data were transformed into standard-deviation scores as described by Tanner et al.,¹⁶ according to the following formula: (measured height - mean height for age) ÷ standard deviation of height for age. The measured adult height was the height measured when the height of a child over 15 years of age had increased by less than 0.5 cm for two consecutive years.

The target adult height was calculated as described by Luo et al.,^{17,18} with the addition of 0.7 cm to the height for boys and 1.0 cm to the height for girls because of trends over time, as $45.99 + 0.78x + 0.7$ cm for boys and $37.85 + 0.75x + 1.0$ cm for girls, where x is the father's height and the mother's height summed and divided by 2.

The primary outcome was the measured adult height in relation to the target adult height. The difference between the meas-

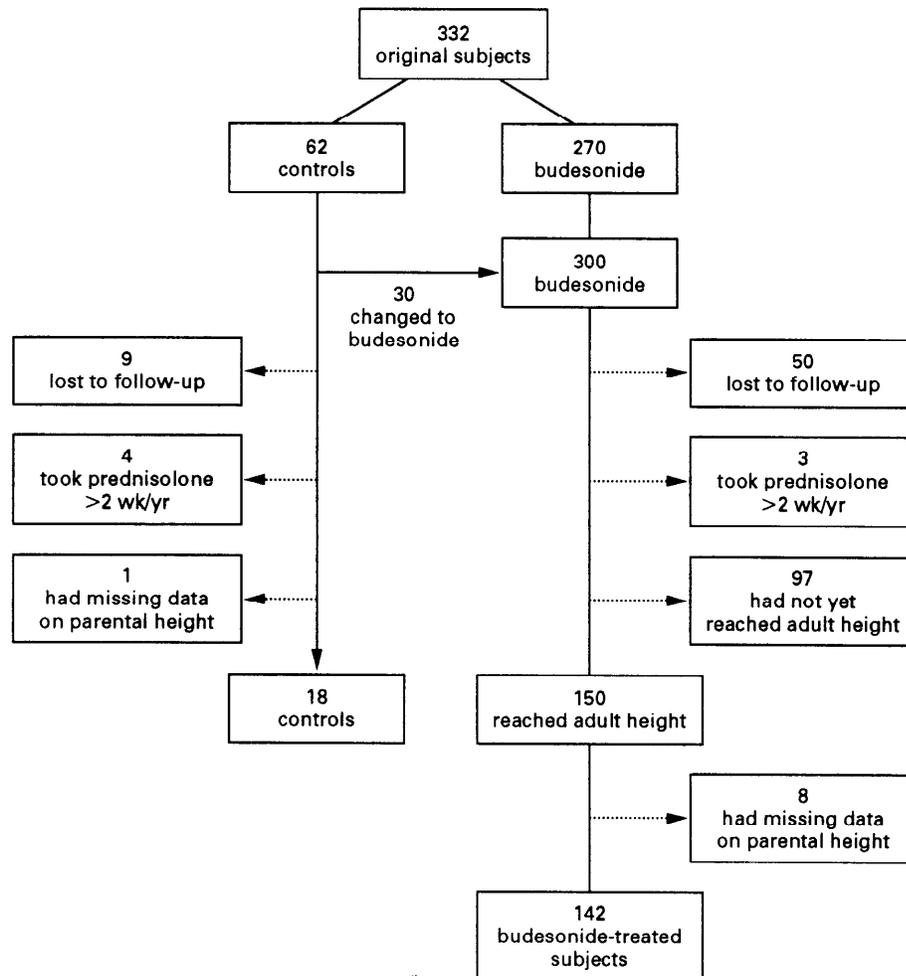


Figure 1. Status of the 332 Children Included in the Study as of August 1999. Only 20 of the 97 children who were excluded from the analysis because they had not yet reached adult height were 15 years of age or older.

TABLE 1. CHARACTERISTICS OF THE STUDY SUBJECTS.

CHARACTERISTIC	BUDESONIDE GROUP AT START OF TREATMENT (N=142)	BUDESONIDE GROUP AT ATTAINMENT OF ADULT HEIGHT (N=142)	CONTROL GROUP AT ATTAINMENT OF ADULT HEIGHT (N=18)	SIBLINGS WHO HAD ATTAINED ADULT HEIGHT (N=51)
Boys/girls — no.	86/56	86/56	11/7	24/27
Age — yr				
Mean	8.7	18.0	18.5	21.4
Range	3–13	16–24	16–22	17–25
Duration of asthma — yr				
Mean	5.3	14.4	14.1	
Range	0.5–12	5–23	3–20	
Prebronchodilator FEV ₁ *				
Mean — % of predicted	69	96	81	
Range — % of predicted	31–101	80–110	62–98	
Value				
≥80% — no. of subjects (%)	64 (45)	140 (99)	11 (61)	
60%–79% — no. of subjects (%)	60 (42)	2 (1)	7 (39)	
30%–59% — no. of subjects (%)	18 (13)	0	0	

*FEV₁ denotes the forced expiratory volume in one second.

ured and the target height was analyzed by the paired-samples t-test. The assumption of normality was examined by probability plot and accepted.¹⁹

We assessed the following secondary outcomes: whether the difference between the measured height and the target adult height depended on the mean daily budesonide dose, the total cumulative budesonide dose, the duration of treatment, the duration of asthma at the beginning of treatment or at the time of attainment of adult height, the use or nonuse of intranasal corticosteroids, the growth rate, the standard-deviation score for height or the forced expiratory volume in one second (FEV₁) before budesonide treatment, and the growth rate and the changes in the growth rate or standard-deviation score for height during the first year of budesonide treatment. The tests were performed by analysis of variance and covariance. All tests were performed for the whole group of children and for girls and boys separately. All reported P values are two-tailed.¹⁹

RESULTS

The budesonide-treated children reached their target adult height (Fig. 2) to the same extent as their healthy siblings and the children in the control group (Table 2). There was no reason to suspect that the 20 children who were older than 14 years of age and who had not yet reached their adult height would attain an adult height markedly less than their target adult height. In all groups, more than 95 percent of the children attained an adult height that was within 9 cm above or below their target adult height.

The mean cumulative dose of budesonide at the time of attainment of adult height was 1.35 g (range, 0.41 to 3.99). The mean duration of budesonide treatment at this time was 9.2 years (range, 3 to 13), yielding a mean average daily budesonide dose of 412 μg (range, 110 to 877). Twenty children in the budesonide group who were more than 15 years old had not yet reached their adult height. Their mean cumulative dose of budesonide (1.25 g; range, 0.40 to 3.12) was not significantly different from that of the chil-

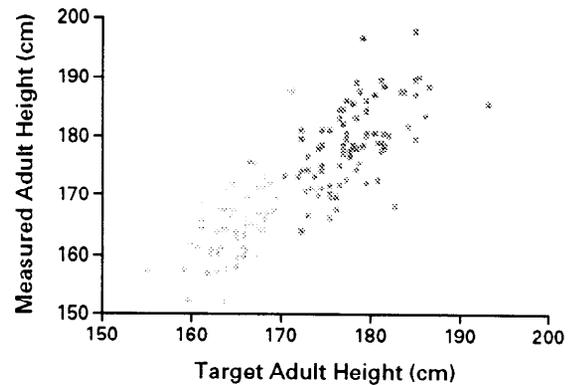


Figure 2. Measured Adult Height in Relation to Target Adult Height in 142 Children Treated with Inhaled Budesonide for 3 to 13 Years. Diamonds represent girls, and squares boys.

dren who had attained their adult height (P=0.72). There was no significant correlation between the duration of treatment (P=0.16) or the cumulative dose of budesonide (P=0.14) and the difference between the measured and target adult heights (Fig. 3).

The difference between the measured and target adult heights was not significantly associated with the subject's sex (P=0.30), age at the beginning of budesonide treatment (P=0.13), age at which adult height was attained (P=0.82), or duration of asthma before the start of budesonide treatment (P=0.37).

The standard-deviation score for height and the FEV₁ as a percentage of the predicted value before the start of budesonide treatment were correlated (P=

TABLE 2. MEASURED AND TARGET ADULT HEIGHTS.*

GROUP	No.	MEASURED ADULT HEIGHT	TARGET ADULT HEIGHT	DIFFERENCE BETWEEN MEASURED AND TARGET ADULT HEIGHTS (95% CI)
Budesonide	142	173.2±9.5	172.9±7.5	+0.3 (-0.6 to +1.2)
Girls	56	164.6±6.0	164.8±3.0	-0.2 (-1.6 to +1.0)
Boys	86	178.8±6.8	178.1±4.3	+0.7 (-0.5 to +1.9)
Controls	18	173.9±10.1	174.1±8.2	-0.2 (-2.4 to +2.1)
Siblings	51	172.3±9.5	171.4±8.7	+0.9 (-0.4 to +2.2)
Girls	27	165.8±5.6	165.2±8.7	+0.6 (-1.2 to +2.3)
Boys	24	179.8±7.2	178.5±4.9	+1.3 (-0.7 to +3.3)

*Patients in the budesonide group had been treated with inhaled budesonide for an average of 9.2 years. Patients in the control group had never been treated with inhaled corticosteroids. The members of the third group were healthy siblings of patients in the budesonide group and had attained adult height. Plus-minus values are means ±SD. CI denotes confidence interval.

0.05), indicating that the severity of asthma influenced growth. Budesonide treatment was associated with a significant change in the growth rate during the first years of treatment, as compared with the run-in period. The mean growth rate was 6.1 cm per year (95 percent confidence interval, 5.7 to 6.5) during the run-in period, 5.1 cm per year (95 percent confidence interval, 4.7 to 5.5; $P < 0.001$) during the first year of treatment, 5.5 cm per year (95 percent confidence interval, 5.1 to 5.9; $P = 0.02$) during the second year, and 5.9 cm per year (95 percent confi-

dence interval, 5.5 to 6.3; $P = 0.53$) during the third year. However, the changes in growth rate during this period were not correlated with the differences between the measured and target adult heights ($P = 0.44$). The initial growth retardation was significantly correlated with age ($P = 0.04$), with a more pronounced reduction in younger children.

The standard-deviation score for height before budesonide treatment and the difference between the measured and target adult heights were correlated ($P < 0.001$), so that children with a low standard-deviation score for height before treatment had a smaller adult height than expected. There was a trend toward an association between the difference between the measured and target adult heights and the duration of asthma at the time adult height was measured ($P = 0.07$).

Forty children in the budesonide group used intranasal corticosteroids for an average of 24 months (range, 6 to 72). The adult height of these children was similar to that of the children who had never used intranasal corticosteroids ($P = 0.99$). Moreover, the difference between the measured and target adult heights was not associated with the cumulative number of months of use of intranasal corticosteroids ($P = 0.72$).

Compliance with budesonide treatment was calculated according to the following formula: $100 \times (\text{number of doses taken} \div \text{number of doses prescribed})$. The mean estimated compliance was 68 percent (range, 49 to 90 percent). The difference between the measured and target adult heights was not associated with compliance ($P = 0.38$).

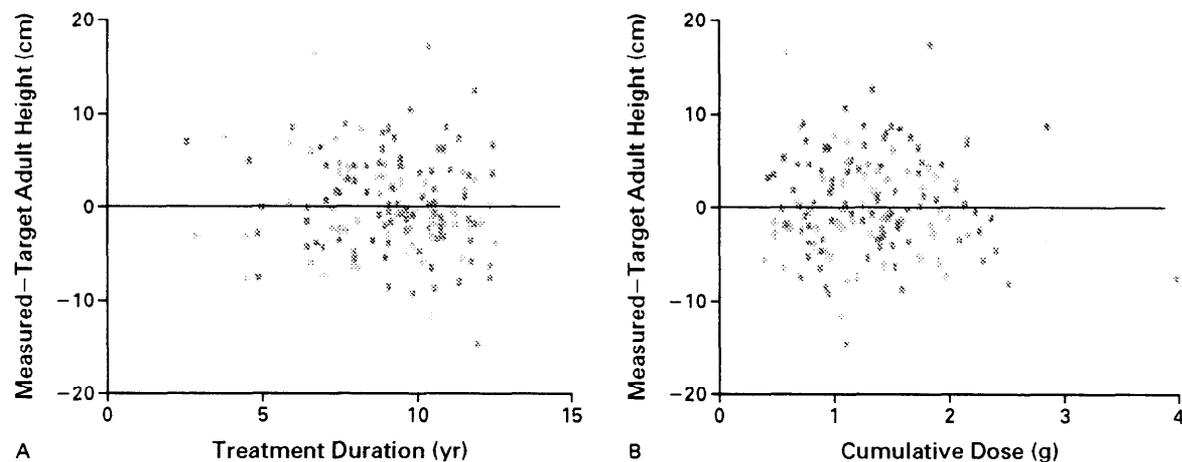


Figure 3. Differences between the Measured Adult Height and the Target Adult Height as a Function of the Duration of Budesonide Treatment (Panel A) and Cumulative Prescribed Budesonide Dose (Panel B).

Diamonds represent 56 girls, and squares 86 boys.

DISCUSSION

We found that children with asthma who had received long-term treatment with inhaled budesonide attained normal adult height. Furthermore, we found no evidence of a dose-response relation between the mean daily dose of budesonide, the cumulative dose of budesonide, or the duration of budesonide treatment and the difference between the measured and target adult heights. Our findings suggest that long-term treatment with inhaled budesonide does not have any clinically important adverse effects on adult height. This corroborates the results of retrospective studies of smaller groups of children treated for shorter periods with inhaled corticosteroids^{20,21} and a prospective study of 66 children who were followed for 13 years until they reached adult height.²²

Normally, 95 percent of the population is expected to attain an adult height within 9 cm above or below their target adult height.¹⁸ This was true for the patients in our study, indicating that great individual sensitivity to the systemic effects of inhaled budesonide was uncommon.

Several studies of growth during a period of one year have reported growth retardation of approximately 1.5 cm per year in children treated with 400 μ g of inhaled beclomethasone per day, as compared with those receiving placebo.²³⁻²⁶ These data have led to the inclusion of warnings about growth retardation in the package inserts for inhaled corticosteroids in the United States. Our results show the effects of continuous treatment for 10 years at the same mean corticosteroid dose as in the 1-year studies. The growth rate during the first year of treatment was on average 1 cm less than that during the run-in period. Thus, our results are consistent with those of shorter studies of beclomethasone. The initial reduction in the annual growth rate did not persist, however, and the adult height was not adversely affected. Furthermore, the initial growth retardation in individual children had no relation to differences between the measured and target adult heights. The reason for the absence of a relation is not clear. Others have also found the growth-retarding effect of inhaled corticosteroids to be more marked during the beginning of treatment.²⁶⁻²⁸ Differences in compliance over time did not seem to be the cause.

Another reason for the discrepancy between short-term studies and studies of adult height could be that pubertal children are less sensitive than prepubertal children to the growth-retarding effect of exogenous corticosteroids, as we and others²⁵ have found. Most growth studies have been performed in children six through nine years of age. Finally, exogenous corticosteroids may retard bone maturation to the same extent that they retard growth.²⁹⁻³² This possibility is difficult to assess in children with chronic asthma, regardless of whether they use inhaled corticosteroids. Such children often have retarded bone maturation,

prepubertal growth retardation, and a delayed onset of puberty.^{22,33-35}

A weakness of our study is that there were few children remaining in the control group by the time they reached adult height. Therefore, we measured the adult heights of healthy siblings of budesonide-treated children, whose genetic growth potential and living conditions were very similar to those of the subjects in the study group. Although a randomized, double-blind design would have been ideal, this was not possible in our 15-year study. The demographic similarities among the various groups suggest that they were reasonably comparable.

Generally, asthma in our patients was well controlled once treatment with inhaled budesonide was initiated. This made it difficult to assess how the severity of asthma influenced growth. The correlation between the FEV₁ as a percentage of the predicted value and the standard-deviation score for height before budesonide treatment suggests that severe asthma may in itself have a negative effect on growth, as observed in other studies.^{36,37} It is less clear whether severe asthma also has an adverse effect on adult height. The strong correlation between the standard-deviation score for height before treatment and the adult height suggests that severe asthma may also adversely affect adult height. This is in agreement with findings in other studies.^{20,34,35} However, many patients in the control group who had more severe disease dropped out of our study. Thus, among those who stayed in the study long enough to have their adult height measured, either the disease was milder or the asthma had gone into remission.

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Growth in asthmatic children treated with fluticasone propionate

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Objective: To determine whether inhaled fluticasone propionate has long-term effects on growth in children with persistent asthma.

Study design: In a double-blind, randomized, parallel-group, multicenter study, 325 prepubescent children with persistent asthma and normal growth rates were treated with placebo or inhaled fluticasone propionate powder 50 µg or 100 µg administered twice daily by a breath-actuated device for 1 year. Growth was evaluated monthly, whereas other safety variables and pulmonary function were evaluated periodically.

Results: The prepubescent patients showed no statistically significant differences in mean height, mean growth velocity, or mean skeletal age between any of the treatment groups at any time. Over a period of 1 year, mean height (\pm SE) increased 6.15 \pm 0.17 cm in the placebo group, 5.94 \pm 0.16 cm in the fluticasone propionate 50 µg group, and 5.73 \pm 0.13 cm in the fluticasone propionate 100 µg group ($p = 0.308$, overall).

Conclusions: Prepubescent children treated with fluticasone propionate 50 µg and 100 µg administered twice daily for 1 year grew at rates similar to placebo-treated control subjects and at rates equal to expected growth velocity for age.

(*J Pediatr* 1998;132:472-7.)

Corticosteroids are the most effective anti-inflammatory medications for patients who have asthma requiring daily, long-term intervention.¹ Chronic treatment with inhaled corticosteroids has been shown to confer many clinical benefits in children with asthma, including a reduction in airway hyperresponsive-

ness,²⁻⁴ improvement in lung function⁵ and asthma symptoms,⁴ and reduction in pathologic structural changes in the airways.⁵ Although prolonged treatment with oral corticosteroids causes undesirable systemic effects, inhaled corticosteroids generally are well tolerated and have been recommended as first-line

therapy for patients with mild or moderately severe, persistent asthma.¹ Despite this endorsement, some concern remains about the potential for inhaled corticosteroids to influence growth in children. Resolving this issue is complicated by the potential for asthma to delay growth and influence bone age, especially if the disease is severe or uncontrolled.⁶⁻⁹

Evidence of growth suppression has been observed in patients taking beclomethasone dipropionate in doses of 400 µg per day or greater^{10,12} in some studies, whereas in other studies, including a meta-analysis of 21 studies,¹³ no significant effect on growth was noted after treatment with beclomethasone dipropionate (up to 600 µg/day) for up to 13 years or after treatment with budesonide (up to 800 µg/day) for up to 6 years.^{6,7,14-16} However, criticisms of the design of these studies have included lack of evaluation of pubertal status; inappropriate assessment of pubertal status by age alone; lack of an adequate untreated control group; lack of baseline growth velocity data; baseline differences in age and height between treatment groups; and reliance on growth monitoring procedures, such as knemometry, which do not accurately predict long-term growth.

Fluticasone propionate is an inhaled corticosteroid that undergoes extensive first-pass metabolism to an inactive metabolite after absorption from the gastrointestinal tract and therefore has negligible oral systemic bioavailability.¹⁷ Fluticasone propionate, at doses of 100 µg/day and 200 µg/day, has previously been shown to be effective and well tolerated in short-term, double-blind^{18,19} and long-

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term, open-label studies²⁰ in children with persistent asthma. Therefore these dosage regimens were selected in the current study, which evaluated the long-term effects (over 52 weeks) of fluticasone propionate powder on growth in children.

METHODS

Patient Selection

Children were eligible for the study if they met the American Thoracic Society criteria²¹ for asthma and had normal growth rates as defined by height measurements (one measurement taken 6 to 18 months before the study and one at screening) between the 5th and 95th centiles and growth velocity between the 10th and 97th centiles (Serono Laboratories, Norwell, Mass.). All height measurements were taken using identical wall-mounted Harpenden stadiometers (manufactured by Holtain, Crymmych, Wales). Patients were prepubescent as defined by a sexual maturity rating of 1 in any Tanner classification.²² The patients had a history of persistent asthma for at least 3 months. The boys were aged between 4 and 11 years and the girls were aged between 4 and 9 years. Patients were excluded if they had received systemic, intranasal, or ophthalmic corticosteroids within the month before study entry, or had cataracts, glaucoma, or any other significant concurrent disease or condition. Previous systemic corticosteroid use was limited to a total of 60 days within the 2 years before study entry. Patients on a maintenance dose of inhaled corticosteroids were required to maintain a fixed dosage regimen for at least 3 months before screening. At screening, the dose of inhaled corticosteroid was not to exceed 8 puffs/day of beclomethasone dipropionate or triamcinolone acetonide or 4 puffs/day of flunisolide. Patients not on a fixed regimen of inhaled corticosteroid were not allowed to use inhaled corticosteroid for more than 60 days within 2 years before screening. All patients or their legal guardians gave informed consent.

Study Design

Nineteen clinical centers participated in this prospective, randomized, double-

blind, parallel-group trial. The protocol was approved by the Institutional Review Board at each center. Patients were required to have a forced expiratory volume in 1 second of at least 60% of the Polgar predicted normal value for age and height.²³ Eligible patients entered a 2-week, single-blind, run-in period to evaluate eligibility to continue to the active treatment period, confirm asthma stability, obtain baseline data, and assess patient compliance with the Diskhaler device (Glaxo Wellcome, Eurekaux, France). Patients taking inhaled corticosteroids or other anti-asthma medications (for example, β_2 -agonists, theophylline, or cromolyn) were allowed to continue taking these medications as needed during the run-in period. Patients had to have stable disease, as determined by the individual investigator, and had to complete the run-in period without requiring oral corticosteroid therapy. Patients also were supplied with albuterol syrup and albuterol inhalation aerosol to be used throughout the study as needed for the relief of acute symptoms.

At the end of the run-in period, eligible patients were stratified according to inhaled corticosteroid use at study entry and randomly allocated to receive fluticasone propionate 50 μ g or 100 μ g, or matching placebo, twice daily via a Diskhaler. Patients also were instructed to discontinue use of their previously inhaled corticosteroids and continue other anti-asthma medications. Compliance was measured at each visit by counting the number of package blisters that were used divided by the number of blisters that should have been used during the interval.

Growth and Other Variables

Patients were evaluated at the beginning and end of the run-in period, after the first, second, and fourth weeks of the treatment period, and then every 4 weeks throughout the 52-week treatment period. Growth was measured monthly and other safety variables were monitored at predetermined intervals. Radiographic determination of bone age of the left hand and wrist was performed at baseline and at weeks 24 and 52; the

radiographs were read and interpreted by a central source (FELS Institute, Yellow Springs, Ohio). Patients who achieved pubescence as defined by a sexual maturity rating of greater than 1 in any Tanner classification during the study were allowed to continue but were excluded from the prepubescent growth analysis. Reports of adverse events were elicited by asking nonleading questions and also by physical, oropharyngeal, and slit-lamp examinations.

Patients were withdrawn from the study because of lack of efficacy if they required more than two 7-day bursts of oral corticosteroids or if the investigator determined that the asthma symptoms were unstable. Female patients also were withdrawn if they became menarcheal. Additional withdrawal criteria included the use of intranasal or inhaled corticosteroids and the use of prohibited anti-asthma medications in addition to study medications for asthma control. Final study assessment was performed at the time of study withdrawal.

Statistical Analysis

Traditional safety analyses were based on data from the intent-to-treat population, comprising all patients exposed to the study drug, whereas the growth analyses were based on the same population minus patients who achieved pubescence during the study. The target enrollment size of 90 patients per treatment group was chosen to provide 80% power of detecting a 1.0 cm per year difference in height velocity between treatment groups.

All statistical tests were two-sided, with treatment differences below the 0.05 level considered statistically significant. Comparisons between treatment groups for nonparametric variables were based on the Cochran-Mantel-Haenszel test, controlling for investigators; comparisons for parametric variables were based on an analysis of variance F test, controlling for investigator. Growth and spirometric data were tested for treatment differences using an analysis of variance F test, controlling for investigator. Adverse events were tabulated by treatment group and analyzed for treat-

Table I. Clinical characteristics and pulmonary function in prepubescent patients at screening

Characteristic	Placebo (n = 87)	FP 50 µg (n = 85)	FP 100 µg (n = 96)
Gender, n (%)			
Female	20 (23)	23 (27)	24 (25)
Male	67 (77)	62 (73)	72 (75)
Age (yr)			
Mean (± SE)	8.1 ± 0.2	8.1 ± 0.2	7.9 ± 0.2
Range	4.2-11.6	4.5-11.9	4.0-11.6
Height (cm)			
Mean (± SE)	127.5 ± 1.2	128.2 ± 1.3	127.2 ± 1.2
Range	98.2-151.8	104.0-152.8	101.2-149.7
Weight (kg)			
Mean (± SE)	27.6 ± 0.8	28.4 ± 0.9	28.0 ± 0.9
Range	13.5-48.8	15.3-59.9	13.5-76.9
Screening FEV ₁			
Prebronchodilation	1.56 ± 0.4	1.56 ± 0.04	1.52 ± 0.04
Percent of predicted (± SE)	89 ± 1	88 ± 1	88 ± 2

FEV₁, Forced expiratory volume in 1 second; all treatments administered twice daily; FP, fluticasone propionate.

Table II. Previous corticosteroid use and concurrent asthma medications at screening

Medication	Placebo (n = 106)	FP 50 BID (n = 111)	FP 100 BID (n = 108)
Previous inhaled steroid history,* n (%)			
Naive	48 (55)	46 (54)	52 (54)
Dependent	39 (45)	39 (46)	44 (46)
Previous oral corticosteroid history,† n (%)	22 (22)	32 (29)	17 (17)
Theophylline	21 (20)	13 (12)	18 (17)
Sodium cromoglycate	45 (42)	40 (36)	33 (31)
Nedocromil	2 (2)	3 (3)	0
Beta-agonists	106 (100)	111 (100)	108 (100)

FP, Fluticasone propionate; all treatments administered twice daily.
*Steroid-naïve patients received no more than 60 days of inhaled corticosteroid treatment within 2 years before and during screening. Steroid-dependent patients used inhaled corticosteroids for at least 3 months before and during screening.
†Patients requiring 20 or more days of oral corticosteroid therapy within 2 years before screening.

ment differences using the Fisher exact test.

RESULTS

Study Population

Three hundred forty-four patients were entered into the single-blind screening period. Nineteen patients were not entered into the double-blind treatment period because of the follow-

ing factors: abnormal ophthalmic findings (4 patients), unstable asthma (3 patients), use of prohibited concurrent medications (3 patients), failure to meet inclusion or exclusion criteria (2 patients), or miscellaneous reasons (7 patients). Of the remaining 325 patients assigned to use the study drug, 57 showed signs of puberty during treatment (placebo, 19; fluticasone propionate 50 µg, 26; fluticasone propionate

100 µg, 12) and therefore were excluded from the growth analyses. The remaining 268 prepubescent patients had similar clinical characteristics at baseline across treatment groups (Table I). The use of concurrent asthma medications during screening also was similar among treatment groups (Table II). Oral corticosteroid bursts in patients who completed the study were comparable among treatment groups (placebo, 25; fluticasone propionate 50 µg, 14; fluticasone propionate 100 µg, 17). Compliance rates ranged between 90% and 94% and were similar across treatment groups. Only 66% of prepubescent patients in the placebo group completed the 52-week treatment period compared with more than 80% of patients in each of the two fluticasone propionate groups. Most of the patients not completing the study in the placebo group were withdrawn because of inadequate asthma control. Twenty-three percent of patients treated with placebo withdrew from the study because of lack of efficacy compared with 2% and 4% of patients treated with fluticasone propionate 50 µg and 100 µg, respectively.

Growth Data (Prepubescent Patients)

Nearly all patients in all three groups grew at normal rates over the entire study. There were no statistically significant differences between treatment groups in any growth parameter at any time. The mean height increases from baseline to 52 weeks were 6.15 ± 0.17 cm, 5.94 ± 0.16 cm, and 5.73 ± 0.13 cm, in patients treated with twice daily doses of placebo, fluticasone propionate 50 µg, and fluticasone propionate 100 µg, respectively ($p = 0.308$, overall) (Fig. 1). At the end of treatment, corresponding values for mean growth velocity were 6.10 ± 0.17, 5.91 ± 0.16, and 5.67 ± 0.13 cm/year with placebo, fluticasone propionate 50 µg, and fluticasone propionate 100 µg, respectively ($p = 0.313$, overall). Corresponding values for mean change from baseline in growth velocity were -0.11 ± 0.15, -0.40 ± 0.20, and -0.46 ± 0.15 cm/year, respectively ($p = 0.380$, overall). These changes in height at the end of treatment were comparable to

normal growth rates for patients of similar age. The numbers of patients who grew at a slightly lower rate (less than 4.0 cm/year) in the placebo, fluticasone propionate 50 µg, and fluticasone propionate 100 µg treatment groups were 0, 3, and 3, respectively.

Skeletal maturation at baseline was comparable to chronologic age at baseline for all treatment groups. At the end of 1 year of treatment, the mean change from baseline in skeletal age was 1.13 ± 0.06 years, 1.13 ± 0.06 years, and 0.95 ± 0.05 years, in patients treated with twice daily doses of placebo, fluticasone propionate 50 µg and fluticasone propionate 100 µg, respectively ($p = 0.146$, overall). No statistically significant differences were observed in the resultant mean skeletal ages across treatment groups.

Other Safety Measures

No significant differences were noted among treatment groups with respect to drug-related adverse events, clinical laboratory tests, and ophthalmologic examinations. One patient treated with fluticasone propionate 100 µg developed a trace of a posterior subcapsular cataract in the left eye at week 24 and was withdrawn from the study. The investigator assessed the event as probably related to the study drug. However, this patient had been treated with inhaled beclomethasone dipropionate and periodic bursts of oral corticosteroids for approximately 2 years before entry into the study. Potentially drug-related adverse events occurred in 8% to 14% of patients in the three treatment groups (Table III).

DISCUSSION

This is the first prospective, 1-year study evaluating the effects of fluticasone propionate on growth in children. The results of this study demonstrate that long-term administration of inhaled fluticasone propionate 100 µg/day and 200 µg/day is well tolerated in children with persistent asthma. No statistically significant differences were noted between fluticasone propionate and placebo treatment groups with respect to height measurement, growth velocity, or

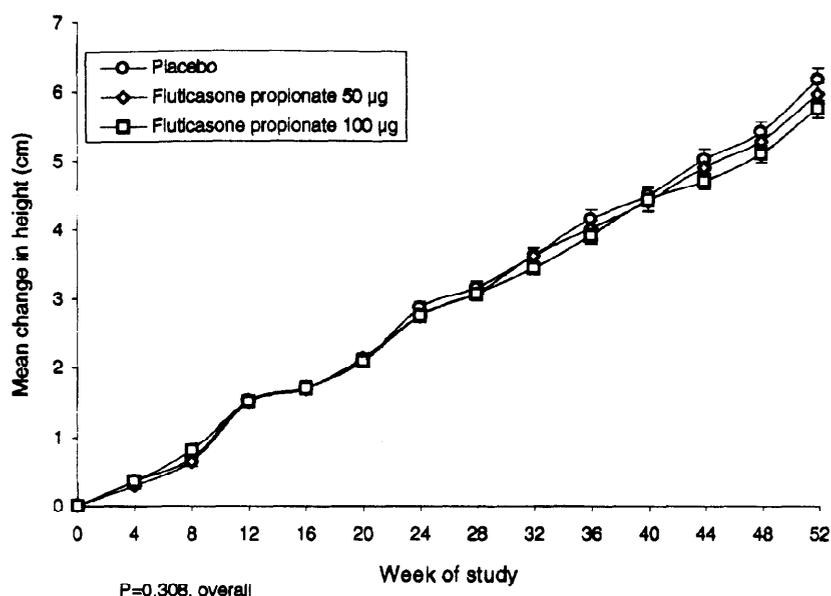


Fig. 1. Mean (\pm SE) change in height in prepubescent patients after treatment with twice daily doses of placebo, fluticasone propionate 50 µg or fluticasone propionate 100 µg for 1 year.

Table III. Drug-related adverse events observed in $\geq 2\%$ of patients

Adverse event	Patients, n (%)		
	Placebo (n = 106)	FP 50 µg (n = 111)	FP 100 µg (n = 108)
Any (n, [%])	10 (9)	16 (14)	9 (8)
Cough (n, [%])	4 (4%)	3 (3%)	4 (4)
Pharyngitis (n, [%])	1 (<1)	4 (4)	1 (<1)
Dysphonia (n, [%])	0	3 (3)	0
Headache (n, [%])	3 (3)	2 (2)	0
Oropharyngeal candidiasis (n, [%])	0	3 (3)	1 (<1)

FP, Fluticasone propionate; all treatments administered twice daily.

skeletal age. During this study, nearly all the patients grew at normal growth rates for children in this age group, regardless of whether they received fluticasone propionate or placebo.

The data presented in the current study are consistent with those of other studies in which growth was not impaired in children who were treated for at least 1 year with inhaled budesonide 200 µg/day¹⁶ or 400 µg/day⁶ or with beclomethasone dipropionate 300 µg/day.¹⁵ In contrast, growth was suppressed in children who received beclomethasone dipropionate 400 µg/day

for 7 months,¹⁰ 400 µg/day for 1 year,¹² or 200 µg/day to 800 µg/day for up to 6 years.¹¹ However, the latter three studies¹⁰⁻¹² have variously been criticized for short duration,¹⁰ lack of assessment of pubertal status,¹² lack of an untreated control group,¹² lack of baseline growth velocity measurements,^{10,12} use of chronologic age versus bone age assessments,^{10,12} and differences between treatment groups in baseline heights and ages.^{11,12} These problems of study design limit the usefulness of the data in providing definitive conclusions regarding an effect on growth in children.

The current study was carefully designed to minimize confounding factors described in the previous studies. This study was prospective, double blinded, randomized, and placebo controlled. Because results can be confounded by the growth rate changes of puberty, prepubescent children were the intended subjects in this study. Age limits were defined separately for boys and girls to prevent patients who were likely to be entering puberty from participating in the study; patients who achieved pubescence during treatment were excluded from the growth analyses. In the current study, prepubescent patients were enrolled only after their growth patterns were confirmed as being normal by at least 6 months of prestudy evidence; large numbers of patients were followed up for 1 year to offset interpatient variability and seasonal variation. All centers used the same equipment and methods to ensure standardized measurements. Bone age assessments and stratification by inhaled corticosteroid use also were included in the design of this study.

A positive relationship between inhaled corticosteroid dose and growth retardation has been observed when sufficient doses are given. Agertoft and Pedersen⁶ evaluated the effect of budesonide on growth in 216 children for 3 to 6 years and found that budesonide reduced growth only when the daily dosage exceeded 400 µg/day. Todd et al.²⁴ reported growth retardation with fluticasone propionate at higher than recommended doses (between 1000 µg/day and 2250 µg/day) in 6 children with severe asthma. In the current study, although there were no statistically significant differences in mean height change, growth velocity, or skeletal age between treatment groups at any time, there was an overall difference of 0.42 cm/year in mean change from baseline in height between prepubescent patients treated with fluticasone propionate 100 µg and prepubescent patients treated with placebo. The numbers of oral corticosteroid bursts in patients who completed the study were comparable across treatment groups. Thus oral corticosteroid use was not an obvious confounding factor in the assessment of

growth in this study. However, these differences could reflect either a small drug effect or withdrawal of poorly controlled, slower growing children from the placebo group because of worsening of asthma control. Patients who remained in the placebo group probably had milder asthma compared with the patients who remained in the active treatment groups. However, it was not appropriate to perform a carry-forward analysis to allow for early withdrawals, because observation of growth for periods of less than 1 year introduces errors resulting from the fluctuations in the growth rate that normally occur in children.

In conclusion, the design of this study evaluating the effect of an inhaled corticosteroid on growth represents the first of its kind to address multiple confounding factors that weakened the results of previous growth studies. The overall results of this study indicate that growth was not significantly impaired in children with asthma after 1 year of treatment with fluticasone propionate 100 µg/day or 200 µg/day. Because the mean growth rate of prepubescent children treated with fluticasone propionate remained normal for age, a trend of slower growth compared with children treated with placebo most likely reflects drop-out of ill, poorly growing children from the placebo group. However, a small drug effect on growth cannot be definitively excluded. Consequently, it remains appropriate to use the minimum effective dose of inhaled corticosteroid in children and to monitor the growth of children by using stadiometry during treatment, particularly at higher doses.

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50 Years Ago in The Journal of Pediatrics

GLOMERULAR FILTRATION RATE, EFFECTIVE RENAL BLOOD FLOW, AND MAXIMAL TUBULAR EXCRETORY CAPACITY IN INFANCY

West JR, Smith HW, Chasis H. J Pediatr 1948;32:10-8

The first half of this century saw enormous advances in our understanding of kidney physiology. Much of this work was based on the knowledge that certain substances were cleared from the body almost completely by glomerular filtration (e.g., mannitol) or tubular secretion (e.g., p-amino-hippurate). Thus the "clearance" (another relatively new concept) of such substances could be used as a measure of glomerular filtration rate (GFR) or renal blood flow. The great renal physiologist Homer Smith and his group were responsible for a large part of this work.

In this study Smith and coworkers undertook careful measurements of GFR and renal blood flow in 23 infants under the age of 2 years in an effort to study the maturation of these functions. Recognizing that increases in GFR or renal blood flow could result from either growth or maturation, they discussed the rationale for "correcting" results for surface area as a way of dissecting out changes caused by maturation. This study provided the information that both measurements, corrected for surface area, reach "adult" values by 1 year of age in normal infants. This concept continues to be recognized as generally accurate.

There is a somewhat disturbing footnote to this work, however. These studies involved the placement of intravenous lines and bladder catheters in healthy infants. Although the authors were careful to thank Dr. Emmett Holt at Bellevue for his "cooperation" in the work, there is no mention of outside ethical review of the undertaking or of the way in which consent was obtained from the parents of the children. It is most unlikely that any contemporary human investigation review board would permit such studies. Fortunately, the protections we accord to infant subjects in research have advanced as much as our understanding of their kidneys!

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Evaluating the effects of asthma therapy on childhood growth

Part I: Principles of study design

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Running head: Asthma therapy and childhood growth

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Abstract

Inhaled corticosteroids are established as the most effective treatment for childhood asthma. However, concerns persist regarding their potential effects on growth and, most importantly, final height.

To assess their effects on growth, inhaled corticosteroids can be compared with placebo (type 1 study), non-steroidal anti-asthma therapy (type 2 study), another inhaled corticosteroid (type 3 study) or “real-life” anti-asthma therapy (type 4 study). Owing to the difficulties in obtaining final height data, several different surrogate measures have often been used: short-term lower leg growth, longer-term statural height growth velocity, childhood height and predicted final height. This paper discusses the choice of endpoint, key trial design issues, including selection and number of subjects in the active and control populations, duration of assessments, methods for measuring height and data analysis, in the context of the different study types.

Specific study design recommendations have been developed following the above, and these principles will be used to guide the interpretation of previously published growth studies.

Introduction

The potent anti-inflammatory effects of corticosteroids rapidly established these agents as the most effective treatment for asthma. However, the systemic effects of oral corticosteroids were soon observed in children, who developed central obesity and reduced growth velocity [1, 2]. This led to the development of methods to deliver corticosteroids directly to the lungs by inhalation and the introduction of inhaled beclomethasone dipropionate in the early 1970s [3, 4]. Drug delivery by inhalation proved to be advantageous as the systemic effects typically associated with oral corticosteroids were reduced to a minimum [5]. Recent data indicate the introduction of inhaled corticosteroids reduces asthma-associated growth suppression, by allowing reduced use of oral corticosteroids and by improving the control of asthma [6]. In the development of treatment regimens to optimize the control of asthma symptoms, there has been a trend for progressively higher doses of inhaled corticosteroids to be used in milder asthma and in younger children.

Inhaled corticosteroids remain the most effective treatment for persistent asthma and are recommended as first-line therapy for children with persistent symptoms [7], although concerns persist regarding their possible effects on childhood growth and particularly any effects on adult height. The interactions of glucocorticosteroids with growth hormone and the regulation of growth are complex. Acute exposure to glucocorticosteroids can enhance growth hormone release [8], but long-term exposure impairs its release [9]. Glucocorticosteroids can also inhibit the effects of growth hormone at target tissues and reduce the activity of insulin-like growth factor-1 [10]. The effect of systemic glucocorticosteroids on growth is thought to be dose-dependent

[11]. Thus, all inhaled corticosteroids could, in theory, cause growth impairment if administered at a sufficiently high dose.

In July 1998 the FDA held a 2-day meeting, reviewing all relevant inhaled and intranasal corticosteroid data with regard to childhood growth [12]. The stated aim was to consider making recommendations about class labelling for these treatments, to safeguard the health and safety of children with asthma requiring such treatment. Of the 55 studies reviewed by the FDA, most were considered to be poorly designed and generally the results of these latter studies showed no effect on growth or were inconclusive. Only four randomized studies of at least 6 months' duration were considered well-designed [13 – 16], and these showed a mean reduction in growth velocity of 1 cm per year compared with placebo or other control ($0.5 - 1.5 \text{ cm}\cdot\text{yr}^{-1}$). These studies also showed a mean reduction in growth velocity standard deviation score (SDS) of 0.58 (0.28 – 0.88).

On this basis the FDA recommended class labelling for all inhaled and intranasal corticosteroids pertaining to the possible effects on growth velocity in children with asthma [17]. They recommended that growth should be regularly monitored by stadiometry in patients receiving these agents, that each patient should be titrated to the lowest effective dose, and that growth studies would be required for all new products and requested for all approved products.

The FDA also recommended the following “gold standard” for the design of growth studies: i) a minimum of 6 months' run-in with height measurements made on at least 3 separate occasions, ii) a minimum of 1 year's randomized treatment to avoid seasonal effects and iii) a 6-month follow up period at the end of the randomized phase during which non-steroidal treatment is administered. Clearly this latter

recommendation poses substantial medical and ethical problems in patients whose asthma is wholly or partly controlled by inhaled steroids, as well as being impractical to conduct and fraught with difficulties in terms of analysis.

Careful consideration of many different factors is required when interpreting the data from growth studies as several aspects of study design can confound the results. In addition, the fact that asthma itself can affect childhood growth further complicates the interpretation of these studies [18 – 20]. Long-term, accurate and precise measurement of growth is necessary to avoid the problems of short-term and seasonal variations in growth velocity. The inclusion of a valid comparator group is also important, while a relatively large number of patients is required to provide appropriate statistical power. In many studies, fixed-dose inhaled corticosteroid therapy is used and, consequently, children whose asthma symptoms are well controlled receive a higher dose than they would do in clinical practice. These and a number of other key issues necessitate careful consideration in designing and interpreting the results of growth studies in children with asthma.

The purpose of this two-part review is to highlight key factors to be considered when designing or appraising studies to assess the effect of inhaled corticosteroid treatment on growth velocity, and to examine the findings of previously published studies. The first part will focus on aspects of study design and provide recommendations for the design of scientifically robust growth studies. The second part will comprise a systematic review of published growth studies, and discuss the design and results of these studies in light of these recommendations.

Factors affecting childhood growth

Childhood growth is a complex process, dependent upon pulsatile, principally nocturnal, release of hormones (principally growth hormone) and, in later childhood, sex hormones [10]. Three distinct post-natal growth phases are identifiable. During infancy, there is a period of rapid growth, with body length typically increasing by 50% in 1 year. The height achieved at the end of this growth phase is principally dictated by genetic and nutritional factors, but birthweight exerts an influence on growth velocity. Prematurely born infants, and some individuals who were small for their gestational age, demonstrate “catch-up” growth during the first year of life, and this process may continue for as long as 2 years. Following infancy, there is a period of gradually decelerating growth that lasts until puberty. During this period, growth is mostly determined by growth hormone secretion alone, and few children cross into different height percentiles. The third growth phase is associated with puberty and consists of an initial period of slow growth (slower than the previous years of relatively steady growth) followed by a growth spurt that lasts about 2 years. Sex steroids and growth hormone control this phase of growth. Importantly, many other factors can affect growth velocity during all phases of childhood growth (table 1), and these need to be accounted for when designing scientifically robust growth studies.

Growth study design classification

At the outset of a clinical trial, it is important to clarify whether the aim is to measure the absolute effect of an inhaled corticosteroid on growth or to compare it with an alternative treatment approach (*e.g.* alternative inhaled corticosteroid, or non-steroidal therapy with or without oral corticosteroid treatment as required). We have devised a

simple classification system for clinical trials assessing growth in children with asthma receiving inhaled corticosteroids (fig. 1). Type 1 studies use a placebo group for comparison with inhaled corticosteroid treatment; type 2 studies use non-steroidal asthma therapy as the comparator; and type 3 studies compare one inhaled corticosteroid with another. Type 4 studies are “real life”, typically observational studies, and the inhaled corticosteroid is compared with any other treatment the patient requires and the dose is adjusted according to asthma control, as is normal in clinical practice (usually, the dose of inhaled corticosteroid is also adjustable). Study types 1 – 3 are randomized, prospective studies and provide direct controlled comparison between treatment groups in the clinical trial setting. However, type 4 studies may not be randomized, and may not be prospective (*i.e.* specific patients may be followed from the beginning to the end of the study, or data on a group of patients may be collected retrospectively using treatment databases). The “trunk” criteria or minimum requirements for all these studies are: statural height measured by stadiometry and a minimum study duration of 1 year. Stadiometry is widely acknowledged as the most reliable means of measuring height, while a study period of 1 year is long enough to avoid potentially confounding seasonal variation in growth, and to establish the presence of a genuine treatment effect.

A type 1 study may provide ideal data for measuring the absolute effect of the inhaled corticosteroid on growth – indeed, the FDA have recommended that this type of study be used for this purpose. However, there are both ethical and statistical problems associated with this approach. Ethically, type 1 studies are only feasible in patient populations with mild – moderate asthma, as placebo is inappropriate for patients with more serious disease, prone for example to significant symptomatic deterioration and exacerbations, and ethical recommendations are continuing to tighten in many

countries. As a result, it is not possible to directly compare high-dose inhaled corticosteroid treatment with placebo in an appropriate patient population. In addition, withdrawal of patients experiencing severe symptoms of asthma is significantly more likely from the placebo group, leading to an imbalance in disease severity in the two groups completing the trial. Since disease severity can affect growth velocity (see section on “Selection of subjects” for more detail) [11, 20] a bias towards greater growth velocity in the placebo group can be expected. An additional source of bias could be improved asthma symptom control in the inhaled corticosteroid group compared with the placebo group, although the effect of this on growth velocity remains to be determined.

Non-steroidal therapies are considered to have no direct effect on growth velocity and the ethical difficulties with this type of study (type 2) are reduced in comparison with the inclusion of a placebo group. However, differential symptom control with steroidal *versus* non-steroidal therapy could bias the results in the same way as for type 1 studies, and to minimize the likely differences type 2 studies are suitable only for patients with mild – moderate asthma. Since oral corticosteroids may be required to control exacerbations, particularly for patients with less mild disease, type 2 studies will likely compare the inhaled corticosteroid with an alternative “treatment strategy” as opposed to strictly non-steroidal therapy. Clearly, all oral corticosteroid use needs to be carefully documented. Another disadvantage of a study comparing an inhaled corticosteroid with non-steroidal treatment is that blinding can be difficult.

Nevertheless, there are medical and ethical arguments in favour of type 2 studies over type 1, as all patients receive some form of anti-inflammatory treatment. Statistically, both type 1 and type 2 studies should be designed to establish at least non-inferior

growth in the inhaled corticosteroid group (*i.e.* one-way equivalence studies; see ‘data analysis’ section).

Type 3 studies are useful in enabling physicians to choose between different inhaled corticosteroids for the treatment of children with asthma. A distinct advantage of these studies is that patients with more severe asthma can be enrolled with a minimum of problems from differential symptom control in the two study groups. Type 3 studies cannot, however, provide information on the absolute effect of a particular inhaled corticosteroid on growth. Also, the use of oral corticosteroids by patients in type 3 studies will complicate the interpretation of the results, as any reduction in growth could be attributed to either form of corticosteroid therapy. Statistically, type 3 studies may be powered to establish non-inferiority or superiority depending on whether the objective is to show that the inhaled corticosteroid is as good as or better than the comparator in terms of any effect on growth velocity (see ‘data analysis’ section).

A weakness of study types 1 – 3 is their use of fixed-dose medication. This is impractical in the long-term and inevitably leads to some patients receiving inappropriate doses – in the case of inhaled corticosteroids this may lead to unnecessary systemic effects and therefore, potentially, reduced growth velocity. By allowing appropriate dose adjustment, type 4 studies are more likely to give a true indication of effects on growth velocity as seen in clinical practice. Also, because a variety of comparator treatments can be used, there is little constraint on the severity of asthma that can be assessed in type 4 studies. This is the most suitable study type for assessing treatment effects on final height. However, a delay of puberty caused by inhaled corticosteroid treatment may not be detected if final height is the endpoint –

height measurement throughout the study is necessary to fully characterize any treatment effects on growth. One of the main difficulties with type 4 studies is statistical analysis. Events such as dose adjustment, use of oral corticosteroids and poor asthma control that could affect growth will occur in most subjects during long-term studies, and it may be expected that not all these events will be fully documented. In addition, if the study is retrospective, differing prescribing practices may have resulted in only the more severely ill patients receiving inhaled corticosteroids and hence again disease and drug effects are confounded. Type 4 studies showing similar outcomes between treatment groups indicate that the inhaled corticosteroid does not impair growth, but if there is a difference between patient groups the difference may not be able to be attributed to the study treatment. Thus, type 4 studies should always be designed to establish non-inferiority as opposed to superiority (see 'data analysis' section).

A further consideration regarding type 4 studies relates to generally accepted treatment guidelines which include 'step-down' therapy for individuals whose asthma has been brought under control. This approach can be adopted to ensure that the study reflects everyday clinical practice, although care must be taken to avoid exacerbations caused by premature or excessive dose reductions. The starting dose may either be fixed for all subjects, or chosen by the investigator according to each patient's requirements.

Growth studies: design criteria

Choosing a parameter to assess effects on growth

It is important that a suitable parameter is chosen to measure the effects of an inhaled corticosteroid on growth. In the long-term, final height is of most interest to physicians, patients and their parents. However, the difficulties of obtaining final height data dictate that suitable surrogate parameters are used. The principal endpoints that have been used in previous studies are reviewed below.

Lower leg growth during childhood

Knemometry is a sensitive technique used to measure short-term changes in lower leg length. The accuracy and precision of knemometry measurements are usually high. However, knemometry data correlate poorly with statural height and tend to overestimate any potential effects on growth [21, 22]. The technique is confounded by movement of dermal water in the lower leg, reducing the accuracy of measurements and questioning the relevance of this parameter as a true growth measurement [23]. In addition, short-term measurement of growth is prone to poor reproducibility due to seasonal variations. Thus, short-term lower leg growth is subject to misinterpretation if an attempt is made to relate the data to long-term statural growth.

Growth during childhood

There is no clear relationship between growth velocity during childhood and final height [24]. However, given the difficulties of obtaining final height data and the lack of sensitivity when measuring height, growth velocity during childhood is an attractive option for assessing the effects of inhaled corticosteroids for study types 1 – 3 (and for short-duration type 4 studies). Assessments of growth velocity must account for all the key sources of variability in growth (table 1), and the choice of an appropriate comparator group is of importance.

Successive measurements of growth velocity are not well correlated because of the cyclical nature of growth over the short- (1-year) and longer-term (2-year) [25, 26]. Given the cyclical nature of growth, control data are essential for any study and, because of the longer-term trends in childhood growth (fig. 2), it would be unwise to incorporate a wide range of ages into any particular study. A wide age range implies a wide range of expected growth rates, increasing the difficulty of detecting treatment effects.

A number of different methods can in theory be used to assess childhood growth. Extrapolation of knemometry data to longer-term childhood growth (*e.g.* annualizing 1-month data) has limited value because of short-term variability in growth velocity [21, 27]. Furthermore, if an inhaled corticosteroid affects growth to a certain extent during the early months of treatment, with growth velocity during later treatment approaching normal (as suggested in some studies) [16, 28] annualizing short-term data would overestimate the effect of treatment on growth. Change in height from the beginning to the end of a long-term study can be used, but the use of just two timepoints considerably increases the potential for inaccurate data due to measurement error. A more accurate estimate of growth rate is obtained by measuring height at a number of timepoints during the study, then performing linear regression of height against time. Growth velocity data are therefore dependent on the precision and accuracy of height measurement, upon which is superimposed the biological variability arising from short- and long-term growth cycles.

Comparison with normal growth values from a population of healthy children is possible, and is one method favoured by regulatory authorities and growth experts, not least because the method allows correction for any intergroup differences in age

or sex distribution. To achieve this, data from the study population are converted to growth SDS. This involves subtracting the “standard” or normal growth velocity for the subject’s age and sex from the observed value in the population, and dividing the result by the standard deviation of the standard population value. The sole focus in this case should be comparison between study groups rather than comparison with a “normal” population, as differences from “normal” values could either be due to asthma itself or to the treatment. For patients with severe disease, who require high-dose inhaled corticosteroid therapy, reduced growth velocity is likely to be observed but cannot simply be interpreted as due to the corticosteroid. Also the effect may not be unacceptable in this population, because poorly controlled asthma may lead not only to impaired growth, but also to serious morbidity or even death. SDS may also be helpful in determining the effect of asthma itself when examining differences in growth velocity between asthmatic patients treated with placebo or non-steroidal anti-inflammatory agents and age- and sex-matched healthy subjects. This is most likely to be applicable in type 1 and 2 studies. “Normal” population data are unavailable for most national populations, making it impossible to account for ethnic or environmental differences that are particularly problematic in multicentre studies. Whatever method is chosen to measure growth, it is important to consider the limitations of all growth velocity data, given the potential variability of growth velocity over time for any individual child.

Height during childhood

Unlike growth velocity, measurement of height at a particular age correlates well with final height [24, 29]. This is not surprising as, although height is dictated by cumulative growth rate, the correlation relates to the probability of an individual

remaining within the same height percentile after a period of time. Successive height measurements are highly correlated, particularly in pre-pubertal children after the age of 3 years, as these children generally remain in the same height percentile until the onset of puberty. Prior to this age, height adjustment from infant levels to the genetically determined percentile causes considerable variability. Height does not provide a sensitive measure of impaired growth for the whole study population, as a reduction in growth velocity may not be manifested as a noticeably low absolute height at the end of a study period. Therefore, height alone is a less suitable parameter than growth velocity for the primary endpoint in study types 1 – 3, and short-duration type 4 studies. However it can be helpful in assessing individual patients whose growth and therefore longer-term height is severely affected by steroidal treatment.

If height is to be used as a study parameter, height at the beginning and end of treatment should be expressed in height centiles with respect to the “normal” population and compared. A shift to a lower centile over the period of the study can be interpreted as evidence of impaired growth.

As mentioned above, the use of just two timepoints increases the potential for inaccurate data due to measurement error. Therefore the accuracy and precision of height measurements made by trained staff using high-quality apparatus becomes even more important.

Predicted adult height

A number of different methods have been used to predict children’s final height. The most commonly used are those of Roche–Wainer–Thissen, Bayley–Pinneau and Tanner–Whitehouse, all three of which require assessment of skeletal maturity [30 – 32]. The 95% confidence intervals of these methods are approximately 7 – 9 cm in

healthy individuals [33]. The accuracy of the Tanner–Whitehouse technique has been optimized by including allowance for parental height as well as height and skeletal maturity [32]. Height alone may be used to predict final height. For healthy children, the 95% predicted interval for final height has been shown to be ± 1.5 SDS (*i.e.* approximately 10 cm) around the value that was predicted using height alone [29]. As with the Tanner–Whitehouse method, the inclusion of mid-parental height improves the estimate predicted final height.

As with height, it is questionable whether corticosteroid treatment would exert a measurable or clinically significant effect on predicted adult height during a study period, particularly if there is a lag between treatment and effect on skeletal ossification. Measurement of the effect of inhaled corticosteroids on predicted final height will be complicated by the fact that asthma itself can delay skeletal maturity and affect childhood growth patterns. In addition, bone age can only be estimated accurately in children aged over 2 years, and height prediction is reliably performed only in children aged over 6 years. Therefore, predicted final height is not considered as a suitable primary endpoint for study types 1 – 3 and short-duration type 4 studies.

Final height

Reduced final adult height is the principal clinical concern and is the preferred primary endpoint for type 4 studies, but is the most difficult endpoint for obtaining prospective data. Measurements of final height have similar accuracy and precision to measurements of height during childhood, but the long duration of final height studies means that such data cannot be obtained until the drug has been available for many years. Prospective, randomized, double-blind studies are impractical and very expensive and complete datasets (including total corticosteroid use, disease control

and severity) are difficult to obtain from retrospective studies. Nevertheless, one large, long-term prospective study has now been performed in children with complete datasets [24]. This showed that treatment of asthma with budesonide had no effect on final height, despite a significant decrease in growth velocity during the first 2 years of treatment.

It is possible to include additional factors to improve the interpretation of data when using final height as the endpoint. The spread of heights in the general population is approximately 23 cm; this can be reduced to around 8 cm if parental height is used and to 4 cm if predicted height is used (the spread of predicted height is dependent on the age at which the estimate is made: approximate values are 7 cm at age 6 – 11, 5 cm at age 12 and 4 cm age 13) [32]. These reductions in error facilitate detection of an effect of corticosteroid therapy on final height by increasing the accuracy of the expected outcome (*i.e.* if future growth remained unaffected). It is therefore recommended that final height is predicted at the outset of all final height studies, even when a non-steroidal control group is included, to maximize the likelihood of detecting a treatment effect. In addition, if parental height is to be used, the same rigorous measurement guidelines as applied to patient measurements should be applied.

Selection of subjects

Age/pubertal status

Growth during puberty is highly variable, usually non-linear and difficult to predict. Therefore, to avoid this problem and obtain a sensitive measure of drug effect, it is necessary for studies measuring growth velocity, change in height or change in

predicted final height to include pre-pubertal children only [34]. Upper age limits should be implemented in these studies to ensure that the subjects' growth is not affected by puberty or pre-pubertal growth deceleration during the study; these are 9 years for girls and 9.5 years for boys. Additionally, sexual maturity should be assessed to ensure pre-pubertal status – the Tanner sexual maturity rating scale is commonly used to achieve this (a rating of > 1 is generally interpreted as onset of puberty) [35]. It is necessary to assess sexual maturity not only at the outset of the study, but also at the end of the study period to ensure that puberty does not affect growth measurements taken during the study. It is advisable to avoid the inclusion of patients with a large age range, as this would create the potential for increased inter-subject variability, due to the cyclical nature of childhood growth and altered accuracy in height prediction [26].

For studies of final height (usually type 4), it is preferable to recruit children who are initially pre-pubertal, to ensure the effects of treatment throughout childhood are assessed. Clearly, children entering puberty during the study are not excluded.

A lower age limit of 4 years is generally appropriate for all study types because of the changing influences of hormonal and nutritional factors on growth velocity in younger children, and the lower age limit is raised to 6 years if predicted adult height is one of the study parameters. However, in some circumstances it is necessary to assess the effect of inhaled corticosteroid therapy in younger children. Children younger than 4 years old should in all cases be studied separately, and care must be taken to account for factors such as birthweight and nutrition. Standing stadiometry is only possible for children who are older than 1 year, though infants' length can be

measured accurately and precisely using an infantometer, which measures the length of the infant lying down.

Severity of asthma/asthma control

To minimize inter-subject variability, it is necessary to recruit children with as narrow a range of asthma severity as possible. The choice of asthma severity depends on the type of study performed. As previously mentioned, only populations with mild – moderate asthma are suitable for type 1 studies. For type 2 studies, mild – moderate asthma is also the least likely to present practical difficulties as it is generally acceptable to treat this population with non-steroidal therapy, and the variation between treatment groups in drop-out rates due to poor efficacy should be smaller. Only type 3 and 4 studies can include patients with higher disease severity, as all study participants may receive effective therapy for asthma. However, children whose disease is too severe to be controlled by inhaled corticosteroids alone are best excluded. These children are likely to receive oral as well as inhaled corticosteroids, which would preclude measurement of the absolute effect of the inhaled corticosteroid. We recommend that no more than four courses of oral corticosteroids are permissible per year in growth studies, as children who receive more than this have demonstrated persistently reduced cortisol responses to adrenocorticotrophic hormone [36].

Aside from the increased requirement for oral corticosteroid treatment, possible reasons for asthma causing growth impairment are: delayed puberty, reduced growth hormone secretion, other endocrine malfunction, decreased appetite and increased energy demands [11, 20]. Additionally, exercise may have a contributory effect, as children with asthma tend to exercise less than those without disease and exercise is

associated with increased growth hormone levels in asthmatic children [37]. In any case, there appears to be a positive correlation between asthma severity and the degree of growth impairment [11, 20]. It is also worth noting that the systemic bioavailability of inhaled corticosteroids is affected by disease severity. In healthy volunteers, pulmonary absorption of inhaled corticosteroids is higher than in patients with asthma, leading to greater systemic bioavailability [38]. Indeed, the evidence indicates that the greater the level of airflow obstruction, the lower the systemic exposure [39]. Therefore, to provide data that are relevant to clinical practice, the effects of high-dose inhaled corticosteroids need to be assessed in patients with appropriately severe asthma. Since type 1 and type 2 studies can only be performed in patients with mild – moderate asthma, high doses of inhaled corticosteroids cannot be compared directly with placebo or non-steroidal therapy.

Besides disease severity, the degree of asthma control may also influence both the treatments required by the patients and their growth. Clearly these two are linked, but some patients may have mild – moderate disease which is not well controlled resulting in symptoms and exacerbations, while patients with more severe diseases may be well controlled on inhaled corticosteroids. The degree of disease control may in such circumstances have as substantial an impact on growth as the underlying disease severity. Ideally, both disease control and disease severity need to be accounted for throughout the study, to ensure that these factors do not affect growth independently of the study treatments.

Height and growth velocity

Children who are exceptionally tall, short, underweight or overweight may inherently have a growth velocity that is different from “standard” values [40, 41]. Thus, only

children with height measurements within the percentile range 5 – 95% of normal values for their age should be included in all types of growth study. Nevertheless, it is worth noting that this precludes children who are already of short stature, in whom any impairment of growth would be of greatest concern. Separate studies in children at the lower end of the normal height range would therefore be desirable.

Patients should also be excluded if they are outside the normal range for growth velocity. For example, Turner's syndrome is associated with reduced growth, which would confound the effects of asthma or therapy on growth. The 10 – 90% percentile range for growth velocity seems to be appropriate for inclusion in clinical trials, but there are currently few data on which to base this conclusion. Selection of patients according to their growth velocity requires a run-in period of at least 12 months, to ensure accurate assessment of growth velocity. Assessment during run-in also enables comparison of growth velocity before and after inhaled corticosteroid treatment. However, such run-in periods pose substantial practical, medical and ethical challenges, particularly if treatment with inhaled corticosteroids is not permitted during this period.

Congenital and environmental factors

Patients with active or historical evidence of endocrine disorders (*e.g.* growth hormone deficiency or thyroid hormone deficiency or excess) should be excluded from all types of growth study. Other exclusion criteria include growth disorders (*e.g.* Turners' syndrome, Klinefelter's syndrome) and systemic diseases likely to affect growth (*e.g.* inflammatory bowel disease, coeliac disease, chronic renal failure). Exposure to cigarette smoke is not necessarily an exclusion factor, but should be recorded for inclusion in the data analysis, as should age of onset of wheezing.

Control population

The control and study populations should be well matched in terms of age, sex, pubertal status, height, growth rate (perhaps using a run-in period for assessment), and asthma severity and disease control at baseline. Other factors that may influence growth rate also need to be recorded at baseline (*e.g.* age of onset of asthma, socioeconomic status, exposure to tobacco smoke). Any differences between the populations can then be accounted for in the analysis of study results.

Differences between delivery devices used by the inhaled corticosteroid and control groups should be minimized, as the dose delivered to the patient's airways and particle size distribution vary between devices, potentially affecting systemic availability [42]. This consideration is most important for type 3 studies, as a true comparison of different inhaled corticosteroids can only be achieved if the delivery device is identical for the two drugs. In practice, this is not always possible, and use of the same type of device (*e.g.* dry powder inhaler, metered-dose inhaler) is the best compromise. Nevertheless, it is known that differences exist between inhalers of the same type from different manufacturers, and this should be borne in mind when interpreting the results [43].

Duration of growth assessment

As growth velocity varies over time, an extended period between the first and last height measurements is required to avoid short-term inaccuracies. One year is recommended as the minimum duration for study types 1 – 3, as this will prevent

seasonal variation from affecting the results. The necessity for measuring height over at least 1 year has been illustrated by a previous study, where estimates for annual growth velocity were derived from height measurements at 0 and 3, 6, 9, and 12 months. These estimates were then compared with the annual growth velocity measured by linear regression of height measurements taken every 6 weeks (fig. 3) [44]. For type 4 studies a minimum period of inhaled corticosteroid therapy needs to be considered. At least 1 year may be appropriate, but there are few data to guide this decision and to some extent the decision will be guided by the objective and primary measure of the study (as in type 1 – 3 studies, age and pubertal status of the subjects may be critical).

Run-in and follow-up periods of 6 months' duration have been recommended by the FDA to allow growth measurements to be made in the absence of inhaled corticosteroid therapy. This would allow growth velocity to be measured before treatment and for any catch-up growth after treatment cessation to be detected, improving the possibility of detecting any effect of the inhaled corticosteroid on growth. Ideally, the duration of the run-in and follow-up periods should be 1 year to avoid the confounding short-term factors described above. However, there are likely to be substantial medical, ethical and practical difficulties with therapy during run-in or follow-up. In some countries, treatment of asthmatic patients with placebo or non-steroidal therapy may contradict national guidelines on asthma therapy. An additional problem arises from patients withdrawing from the study due to poor disease control during run-in. This may bias the study population towards patients with more mild asthma, perhaps excluding a sub-set of patients who may be more or less sensitive to the effects of inhaled corticosteroids on growth. A follow-up period with discontinuation of corticosteroid therapy is ethically difficult to justify, and any

variability of treatment and disease control during this period would make the results very difficult to interpret.

Measurement of height

A statement on height quality control assurance is essential in all studies. The optimal method for measuring statural height to assess long-term growth is stadiometry, assuming the subject is at least 2 years of age. Each participant should be assigned to a particular nurse for height measurement at every visit, to minimize any scope for interindividual variation [45, 46]. In one study, the coefficient of variation when the height of 22 individuals was measured by one observer (individuals measured five times) was 0.09, compared with 0.16 when individuals were measured by five different observers [44]. Other measures to ensure consistency include using standardized equipment, measuring height at the same time of day at each visit (to avoid potential variability from height decrease during the course of the day) [45], and development of a protocol for height measurements. The written protocol should include details such as the necessity of wearing hair down, ensuring that subjects have bare feet and that body stature is consistent (*e.g.* unstretched chin level) [45, 46]. Height measurements should be made in triplicate, ideally with blinding to remove any bias associated with previous values, and the mean of the three values carried forward for analysis [47]. Modern, digital stadiometers are capable of measuring height to the nearest 0.1 cm.

Measurements should be taken approximately every 3 months to optimize the accuracy of growth assessment. If it is desired to assess whether the effect of corticosteroid treatment on growth occurs only in the first few weeks of treatment, more frequent measurements should be taken at the beginning of the study.

Young infants' statural height, up to the age of 1 year, is measured in the supine position using an infantometer or kiddimeter. As with stadiometers, digital apparatus is available to measure infants' length with an accuracy of 0.1 cm. However, the use of this apparatus introduces another complication due to an increase in measured height of up to 1 cm compared with using a stadiometer [48].

In general, methods of measuring statural height other than stadiometry or infantometry have not been standardized and are less reliable, although a recently developed portable apparatus using ultrasound to measure statural height has been shown to have accuracy approaching that of stadiometry [49].

Data analysis

Growth velocity

To determine the number of study participants required to power the study adequately, it is necessary first to identify the minimum intergroup difference that needs to be detectable (*i.e.* minimum detectable difference). This is determined initially by whether the study is seeking to establish non-inferiority or superiority. Growth studies are distinct from efficacy studies in that non-inferiority is sought in placebo-controlled trials (*i.e.* study types 1 and 2); superiority is sought only in studies comparing one inhaled corticosteroid with another. In our opinion, based on clinical practice and evidence from previous studies [34,50], an intergroup difference of $0.8 \text{ cm}\cdot\text{yr}^{-1}$ should be detectable to establish superiority (type 3 studies). When studying efficacy, half the treatment effect is generally used to define the range for equivalence [51]. This suggests that the minimum detectable difference for non-inferiority growth velocity studies (*i.e.* study types 1, 2 and non-inferiority type 3

studies) should be $\pm 0.4 \text{ cm}\cdot\text{yr}^{-1}$. However, the validity of applying principles used for efficacy studies to the context of safety studies is not known. Table 2 provides an indication of the patient numbers required to deduce non-inferiority or superiority for a range of minimum detectable differences in growth velocity for each study type, with 90% power and based on a standard deviation of no more than $1.4 \text{ cm}\cdot\text{yr}^{-1}$ [34, 50]. It should be noted that the numbers in Table 2 are a guide only, and patient numbers would increase if the data were expected to be more variable. For example, if the standard deviation were $2.8 \text{ cm}\cdot\text{yr}^{-1}$, the patient numbers would quadruple (*e.g.* 1029 patients per group needed to establish non-inferiority with a minimum detectable difference of $0.4 \text{ cm}\cdot\text{yr}^{-1}$ for study types 1 and 2).

For studies using growth velocity expressed in SDS as the primary endpoint, the sample size may be expected to be slightly smaller than for $\text{cm}\cdot\text{yr}^{-1}$, as SDS account for variation due to age and sex. We calculated SDS ranges for males aged 3 and 10 corresponding to the minimum detectable differences used previously ($\text{cm}\cdot\text{yr}^{-1}$), and assumed the middle of this range could be taken as the minimum detectable difference (SDS) for most studies. Table 3 provides an indication of the patient numbers required to detect a range of intergroup differences in growth velocity (SDS) for each study type, with 90% power and based on a standard deviation of no more than 1.5 SDS [34, 50]. Unexpectedly, the variability from these two studies (and therefore sample size estimates) increased when using growth velocity SDS as opposed to growth velocity in $\text{cm}\cdot\text{yr}^{-1}$. This is likely due to the fact that the standard charts from which SDS are derived are based on healthy children rather than children with asthma, and hence may not accurately reflect the population being studied.

Patient numbers are not included in the sample size tables for type 4 studies using growth velocity as the primary endpoint because there are insufficient data from studies of this type to estimate the variability reliably.

Comparison of the inhaled corticosteroid group with the control group is generally the main focus of the data analysis, regardless of the study type. Conversion of height data to growth velocity ($\text{cm}\cdot\text{yr}^{-1}$) can be done quite simply by constructing a regression slope for each patient using all height measurements taken at baseline and during the treatment period. The estimate of growth velocity for each patient is taken as the gradient of this slope (*e.g.* $5 \text{ cm}\cdot\text{yr}^{-1}$). The greater the number of data points, the better the estimate of growth velocity. These data can then be analysed using analysis of covariance techniques including terms for congenital and environmental factors as described above. A more elegant alternative that eliminates the need to calculate a regression slope for each patient is to fit a mixed effects model, where subject effects are assumed to be random and all other effects are considered as fixed. Height is regressed on treatment, time plus other covariates, and the treatment by time interaction tests whether the treatments have different effects on growth velocity. In this type of analysis, subjects with more variable data, perhaps due to fewer height measurements because of early withdrawal, are given less weight in the analysis. Care should be taken with employing this method when dropout from the trial is not random (*e.g.* due to inferior comparator treatment).

Childhood height and predicted final height

Childhood height and predicted final height are not recommended as parameters for primary endpoints, but as supporting analyses for study types 1 – 3, and type 4 studies not measuring final height. For childhood height, the principal aim is to detect any

shift in patients' height centile during the study. This is achieved by comparing individual subjects' height centile at the beginning and end of the study. To analyse study data, height centile at the end of the study can be plotted against height centile at the outset of treatment, and the correlation can be compared between treatment groups. Additional analysis can be performed by comparing, using logistic regression analysis, the proportion of children in each treatment group whose height centile shifts by a predefined number of centiles after treatment. An increase in the proportion of children whose height fell by more than one centile, for example, suggests impaired growth.

Predicted final height data are analysed using the same principles as for childhood height.

Final height

For final height studies, as with growth velocity studies, the first step towards calculating patient numbers for adequate statistical power is to determine the smallest difference that is needed to establish superiority of one treatment over another. Based on clinical experience and evidence from previous studies, a difference in final height of 5 cm would seem appropriate and reasonably convincing as a potential treatment effect. Final height studies (type 4) should be designed to establish non-inferiority and therefore, in keeping with the principles applied for growth velocity above, the equivalence range should be half the treatment effect. As previously mentioned, however, the validity of applying principles from efficacy studies to this setting is not known. Table 4 provides an indication of the patient numbers required to establish non-inferiority for a series of minimum detectable differences, with 90% power and based on a standard deviation of no more than 7.5 cm (the standard deviation for final

height studies ranged from 4.8 to 7.5 cm, reflecting a lack of consistency in the design of these studies) [24, 52 – 55]. Using a childhood prediction of final height reduces the variability, and previous studies indicate that final height minus predicted final height has a standard deviation of no more than 6.0 cm [54, 55]. This reduction in standard deviation may appear small, but the two studies for which predicted final height data are available did not use skeletal age in the prediction, and the study protocols were not wholly stringent. Nevertheless, as shown in table 5, the numbers of patients needed to power the study decreased by approximately one third compared with studies without final height prediction.

If predicted final height is measured for participants in final-height studies, the main aim of data analysis is to firstly obtain a comparison of actual *versus* predicted final height for each patient, and then compare treatments by assessing whether one treatment group creates a greater shortfall from predicted final height. In the absence of predicted height data, it is only possible to compare the final-height data between the treatment groups. Gender and nationality should be accounted for in the analysis, either through the use of final height SDS scores or as covariates in the statistical model. Analysis of covariance techniques should be used to compare treatment groups for both final height and actual *versus* predicted final height, including appropriate environmental covariates.

Populations to be analysed

Both the intent-to-treat and per-protocol populations should be analysed in all growth studies (the per-protocol population should be pre-defined at the start of the study and should exclude any protocol violations that could affect patients' growth assessment).

For study types 1 – 3, it is recommended that subjects who reach puberty at any point during the study are excluded from all data analysis, because of the marked and often unpredictable effects that this physiological state has on growth (pre-pubertal slowing and pubertal growth spurt), potentially confounding treatment effects. An interesting alternative would be to analyse the results of subjects going into puberty during the study separately, with the specific aim of increasing our understanding of any potential effects of corticosteroids on growth during puberty.

For subjects discontinuing study therapy, post-withdrawal growth data for the entire study duration should be included, if possible, in a supplementary mixed-model analysis, as this can eliminate some of the problems arising from a higher dropout rate in the control population. This approach may also provide comparative “real-life” data with alternative therapies that are used in clinical practice.

Possible effects of the degree of asthma control on growth velocity should also be considered. For example, sub-analysis of growth data could be carried out according to the number of exacerbations or a pre-defined level of asthma control, particularly taking into account the level of exercise and normal physical activities that the subjects engage in (although such analysis needs to be stated a priori). Asthma control should therefore be recorded during the study according to pre-defined criteria.

Conclusions

A large number of factors can potentially confound the results of studies assessing the effect of inhaled corticosteroid treatment on growth in children with asthma and it is important to be aware of all these factors when designing or interpreting such studies. The study objectives affect the influence of some confounding factors and we have

devised a new and simple classification system for growth studies to assist in the development of design recommendations that are appropriate for individual studies. The next step is to apply these principles to the interpretation of previously published growth studies, and this is the aim of the second part of this review.

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Table 1. – Potential confounding factors in studies evaluating the effects of asthma therapy on childhood growth.

Psychosocial deprivation	Nutrition	Congenital disease (<i>e.g.</i> Klinefelter's syndrome, Turner's syndrome, growth hormone deficiency)
Age	Birthweight (affects growth during infancy)	Age of onset of wheezing
Puberty	Socioeconomic status	Severity of asthma symptoms
Gender	Seasonal variations in growth (annual)	- well-controlled asthma has less effect on growth than poorly controlled asthma;
Ethnicity	Long-term oscillations in growth (<i>e.g.</i> mid-childhood growth spurt)	- systemic absorption of inhaled corticosteroids is reduced among patients with severe asthma
Parental height	Administration of systemic corticosteroids for asthma or other diseases	Other chronic disease (<i>e.g.</i> inflammatory bowel disease, chronic renal disease, coeliac disease)
Circadian variations (daily)	Administration of topical corticosteroids for eczema or allergic rhinitis	
Compliance with corticosteroid medication		
Exposure to tobacco smoke		

Table 2. – Patient numbers required to detect between-group differences in growth velocity ($\text{cm}\cdot\text{yr}^{-1}$) for different types of growth study.

Study type*	Study objective	Minimum detectable between-group difference ($\text{cm}\cdot\text{yr}^{-1}$)	Minimum number of patients per treatment group [†]
1	Non-inferiority	0.3	458
1	Non-inferiority	0.4	258
1	Non-inferiority	0.5	165
2	Non-inferiority	0.3	458
2	Non-inferiority	0.4	258
2	Non-inferiority	0.5	165
3	Superiority	0.6	115
3	Superiority	0.8	65
3	Superiority	1.0	42
3	Non-inferiority	0.3	458
3	Non-inferiority	0.4	258
3	Non-inferiority	0.5	165

*See figure 1 for growth study design classification (*i.e.* types 1 – 4).

[†]Based on 90% power, 5% significance level and standard deviation of not more than $1.4 \text{ cm}\cdot\text{yr}^{-1}$ [34, 50].

Table 3. – Patient numbers required to detect between-group differences in growth velocity SDS for different types of growth study.

Study type*	Study objective	Minimum detectable between-group difference (SDS)	Minimum number of patients per treatment group [†]
1	Non-inferiority	0.3	525
1	Non-inferiority	0.4	296
1	Non-inferiority	0.5	189
2	Non-inferiority	0.3	525
2	Non-inferiority	0.4	296
2	Non-inferiority	0.5	189
3	Superiority	0.6	132
3	Superiority	0.8	74
3	Superiority	1.0	48
3	Non-inferiority	0.3	525
3	Non-inferiority	0.4	296
3	Non-inferiority	0.5	189

*See figure 1 for growth study design classification (*i.e.* types 1–4).

[†]Based on 90% power, 5% significance level and standard deviation of not more than 1.5 SDS [34, 50].

Table 4. – Patient numbers required to establish non-inferiority in final height studies.

Minimum detectable difference (cm)	Minimum number of patients per treatment group [†]
1	1182
2	296
3	132
4	74
5	48

[†]Based on 90% power, 5% significance level and standard deviation of not more than 7.5 cm [24, 52, 53, 55].

Table 5. – Patient numbers required to establish non-inferiority in studies using final height minus predicted final height.

Minimum detectable difference (cm)	Minimum number of patients per treatment group[†]
1	756
2	189
3	84
4	48
5	31

[†]Based on 90% power, 5% significance level and standard deviation of not more than 6.0 cm [54, 55].

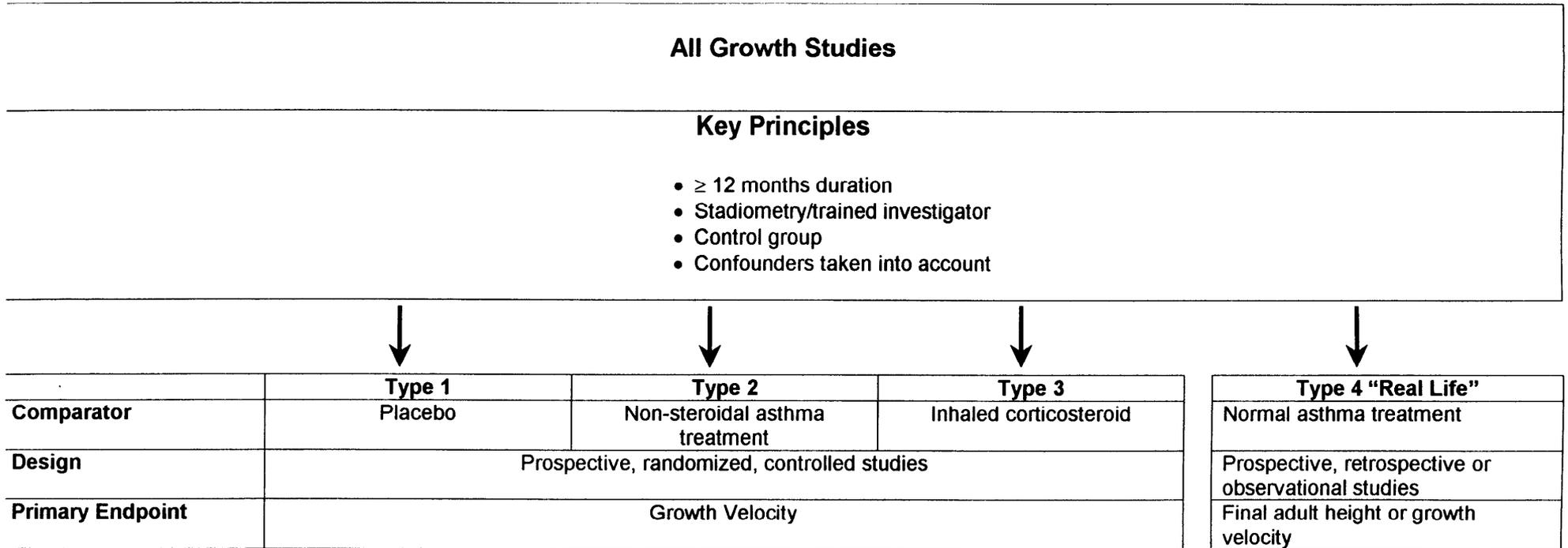


Fig. 1. – Classification of growth studies in children with asthma.

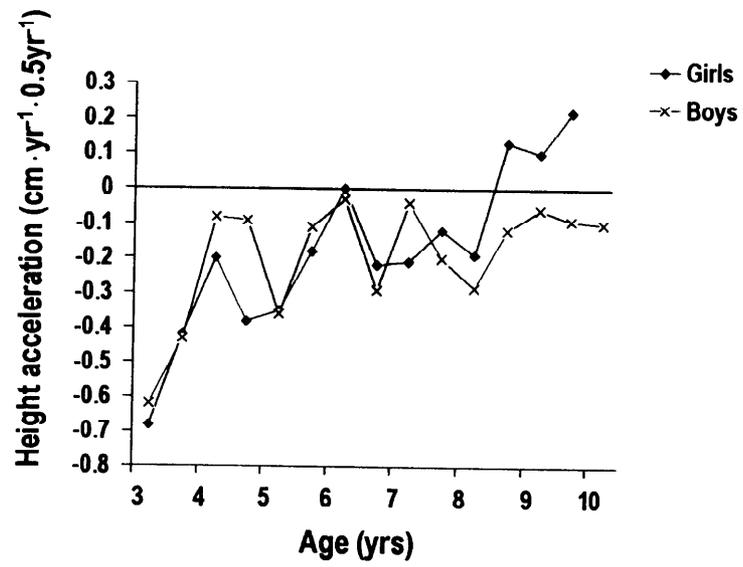


Fig. 2. – Cyclical patterns in childhood growth [26]. (Reproduced with permission from Taylor & Francis Ltd, <http://www.tandf.co.uk/journals>).

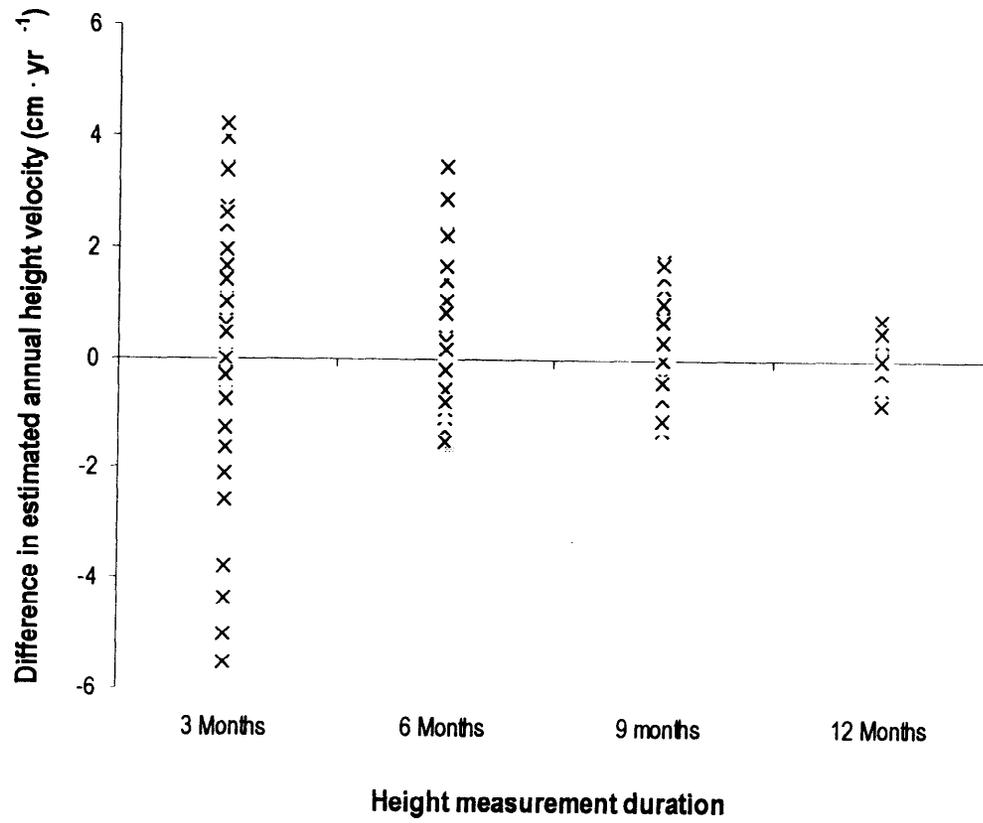
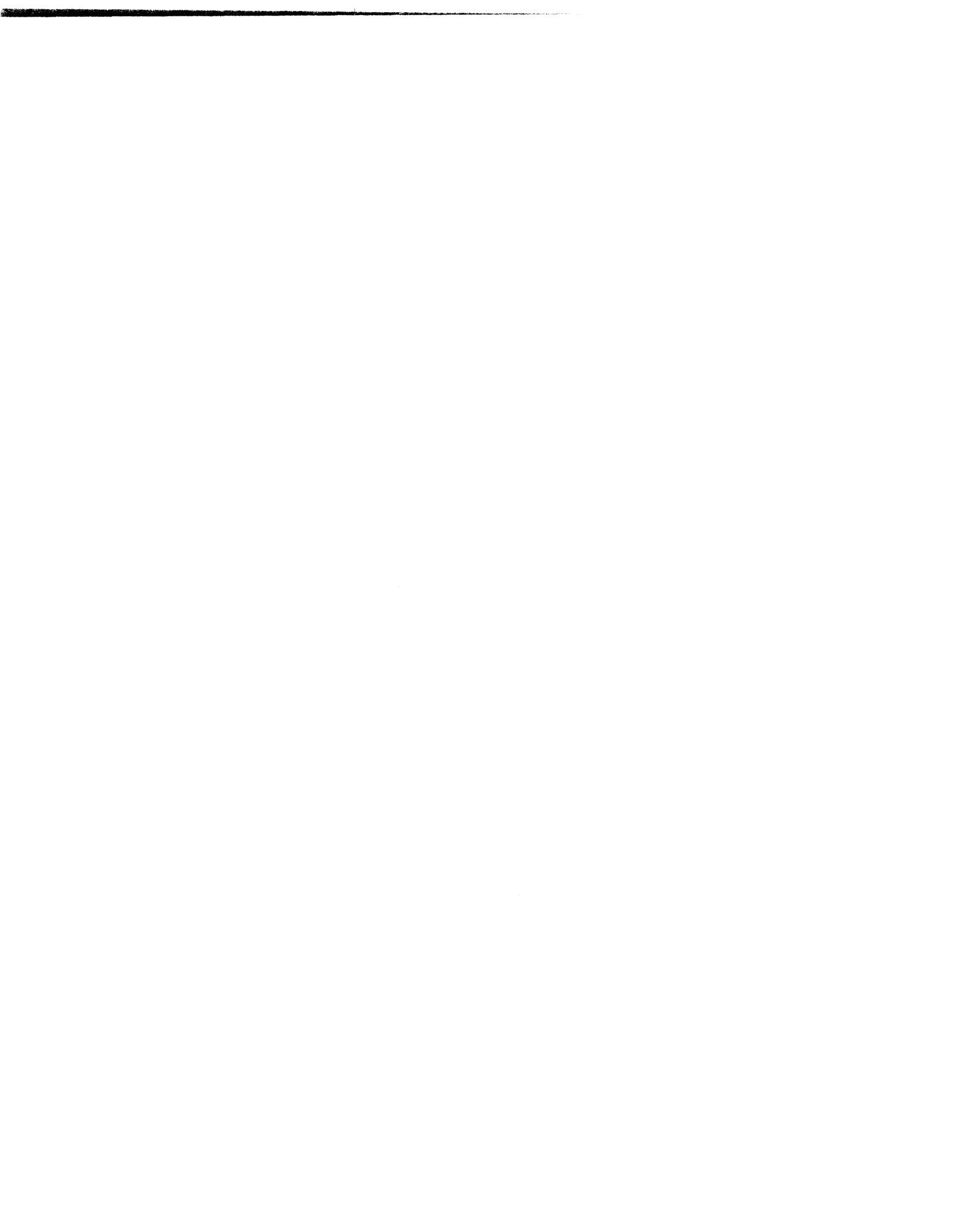


Fig. 3. – Differences in estimated annual growth velocity between two-point analyses based on different durations of height measurement compared with the estimate from 1 year regression analysis [44].



Diurnal variation in stature: is stretching the answer?

L D Voss, B J R Bailey

Abstract

Aims—To investigate the extent and timing of diurnal variation in stature and to examine the effectiveness of the stretched technique in reducing the loss in height.

Setting—A Southampton school.

Design—Fifty three children, divided into two groups, were measured by two independent auxologists using a Leicester height measure. Each child was measured four times, at 0900, 1100, 1300, and 1500, using both an unstretched and a stretched technique.

Outcome measures—Height loss after each of the three time intervals for both unstretched and stretched modes.

Results—There was a clear decrease in stature during the morning, but no further loss occurred after the subjects had been up for around six hours. The mean height losses for the unstretched (stretched) modes were 0.31 cm (0.34 cm) and 0.20 cm (0.23 cm) for the periods 0900 to 1100 and 1100 to 1300, respectively, but only 0.045 cm (-0.019 cm) from 1300 to 1500. Stretching did not reduce the effects of diurnal variation, but significantly affected the recorded height by an average of 0.28 cm. There was no significant difference in reproducibility using either technique (SD 0.30 cm stretched *v* 0.31 cm unstretched).

Conclusions—Diurnal variation in stature may substantially affect the reliability of height data and careful consideration should be given to the timing of repeat measurements. As most height loss occurs in the morning, afternoon clinic appointments would be preferable. The standard stretched technique does not appear to reduce diurnal variation, nor does it affect precision. Measurements made using an unstretched method are recommended to avoid interobserver differences, known to occur where different observers are used. (*Arch Dis Child* 1997;77:319-322)

Keywords: diurnal variation; height measurement; measurement technique

The importance of minimising measurement error in the assessment of growth has been well documented.¹⁻⁴ One potentially significant source of error, diurnal variation in stature, first noted in 1724,⁵ has, however, been largely ignored in clinical practice. Early studies, reviewed by Redfield and Meredith⁶ and Boyd,⁷ were conducted with varying degrees of scien-

tific rigour, but did confirm the presence of diurnal variation in the adult. Most agreed that the total loss amounted to between 2 and 3 cm, and the evidence suggested that the greater proportion of the decrease in height was occurring in the trunk.

Similar effects have been shown in children,⁸⁻¹³ some studies also showing that much of the height loss can be restored by taking a short nap.^{7, 14} Almost all reports agree that the greater proportion of the decrease in stature appears to occur soon after rising,^{6, 9, 10, 12} though it is assumed that, without a nap, further loss continues throughout the day.

There is some disagreement about the total daily loss to be expected, but no two studies have measured their subjects over exactly the same period. Some studies used so few children that their results are dependent on the particular characteristics of those individuals. Even in studies using larger numbers, one found a mean decrease in height of 1.54 cm in 100 children between rising and late afternoon, whereas another found a mean decrease of just 1.0 cm in 70 boys between early morning and bedtime.^{8, 10}

At the end of the last century attempts were made, largely by the physical anthropologists, to standardise the method of measurement.¹⁵ Technique has changed little over the years, clinicians showing little interest in the subject. A stretching technique did become widely adopted about 20 years ago, however, after Whitehouse *et al* suggested that 'gentle upward pressure on the mastoid processes' could minimise the effects of diurnal variation.¹¹ Indeed, these authors claim to have shown that, using this technique, loss in stature between morning and afternoon, though not entirely eliminated, can be reduced to a maximum of 0.46 cm. Thomsen *et al* have compared the precision or reproducibility of the stretched and unstretched methods and report no difference.¹⁶

The aims of the present study were twofold: (a) to ascertain the time of day at which height loss effectively ceases; and (b) to examine the effectiveness of stretching in reducing diurnal variation in height.

Subjects and methods

Fifty three children, aged from 3 years 1 month to 11 years 0 months were divided into two groups of 27 and 26 and were measured by two independent, experienced auxologists (LDV and PM). Each subject was measured on four occasions close to 0900, 1100, 1300, and 1500, always by the same observer (LDV or PM), using the Leicester height measure. The preci-

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sion of this instrument has already been reported.⁴ On each occasion the subjects lined up in random order and were measured twice. The first measurement used an unstretched technique whereby the subject was placed in the correct position, with the head in the Frankfurt plane, but no further contact was made with the child, nor any verbal instructions given, while the cursor was brought down to rest on the child's head. With the child still standing in the same position, the second measurement was made with the observer placing both hands under the child's mastoid processes and applying the usual gentle upward traction. This procedure allowed investigation of the errors involved in the measurements and, in particular, their correlation. All measurements were 'blind'—that is, an independent recorder noted the heights on every occasion, giving the measurer no feedback on performance.

To be able to pool the data from the two observers, a further group of 20 children was measured, on one occasion only, by both auxologists (LDV and PM), each on her own stadiometer, in both the unstretched and stretched positions. This allowed the estimation of any differences in the mean heights achieved on the two instruments so that any necessary corrections could be made to the data arising from the main group of 53 children.

Results

The measurements on 20 children made by both auxologists revealed that one of them (LDV) produced a mean height greater than the other (PM) by 0.20 cm in the unstretched position and 0.18 cm in the stretched. The near equality of these two values suggests a slight difference in the settings of the two instruments being used, despite their being self-calibrating, rather than a difference in measuring techniques. Moreover, as the two values were significantly different from zero ($p = 0.027$ and $p = 0.015$, respectively), the heights obtained by PM were increased by the above amounts in the ensuing analysis. (As this is based essentially on differences between height measurements, it is immaterial whether one auxologist's observations are increased or the other's decreased.)

Table 1 summarises the results of the main experiment with the 53 children. The mean height losses between 0900 and 1100 and between 1100 and 1300 were highly significantly different from zero ($p < 0.001$) whether measured in the stretched or unstretched mode. The mean for the second of these intervals was noticeably smaller than for the first. By the end of the second interval the children's heights effectively levelled out so that the height loss between 1300 and 1500 did not differ significantly from zero ($p=0.44$ for unstretched, $p=0.75$ for stretched). The mean (range) loss over the whole six hour period was 0.555 cm (1.9 to -0.4 cm) unstretched and 0.551 cm (1.8 to -0.6 cm) stretched. Figure 1 shows the individual losses.

Table 1 Mean height loss of 53 children over three two hour time intervals, together with the accumulated six hour loss for unstretched and stretched modes. The SE of each entry is 0.059 cm, for each unstretched decrement, or 0.060 cm, for a mean stretched decrement

Period	Mean height loss (cm)	
	Unstretched	Stretched
0900-1100	0.31	0.34
1100-1300	0.20	0.23
1300-1500	0.045	-0.019
0900-1500	0.555	0.551

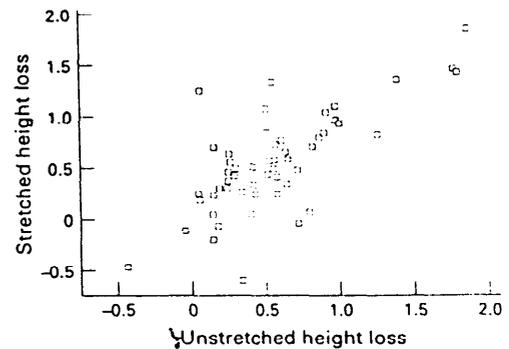


Figure 1 Scatter diagram of total height loss (cm) recorded on 53 children between 0900 and 1500, measured in stretched and unstretched modes.

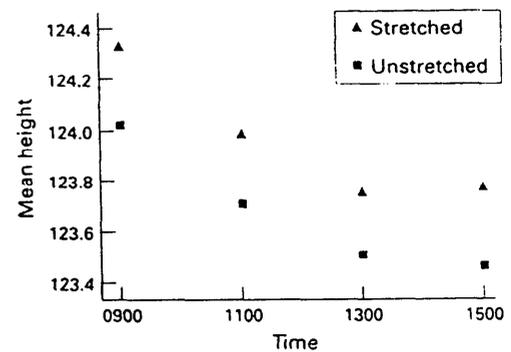


Figure 2 Mean heights (cm) of 53 children, aged 3-11 years, measured on four occasions during the course of one day, using both stretched and unstretched techniques.

Figure 2 clearly shows that, on average, stretching added a constant amount to the unstretched height, but did nothing to reduce the diurnal loss of height. The degrees of stretching on the four occasions did not differ significantly ($p = 0.39$), with the result that the effect of stretching can be said to have increased the height, on average, by 0.28 cm in this experiment. (In view of the large number of observations it would be possible to construct a narrow confidence interval around this value. This would, however, be of use only to the two particular auxologists who carried out these measurements because, as we have described previously, different measurers can effect quite different degrees of stretching on their subjects.^{2,4})

The SD of a single stretched height measurement found in the main experiment, 0.31 cm, is compatible with the value (0.25 cm) found by us previously.^{2,4} The SD for a single unstretched measurement, 0.30 cm, might be expected to be somewhat smaller. The extra variability arising from the stretching

procedure is, however, offset by the negative correlation between the unstretched height and the extension due to stretching, estimated to be -0.32 . A child who happens to stand tall on a particular occasion cannot be stretched by as much as when standing in a more relaxed manner.

Discussion

These results have important implications regarding current practice and the assessment of growth, particularly for the individual child. Firstly, little consideration is ever given to the timing of follow up visits to the clinic. Secondly, while training in measurement techniques is usually considered to be essential, little attention has been paid to the problem of interobserver error.

The present data confirm both the existence of diurnal variation and that the greater proportion of the height loss occurs during the earlier part of the day. Over the period 0900 to 1500 we found an average decrement of around half a centimetre, though several children lost well over 1 cm regardless of the method used (fig 1). On average, the largest decrement occurred during the first time interval, 0900 to 1100. Had we been able to measure the children immediately after rising, the period before 0900 would almost certainly have seen the greatest loss of height, but as few clinic appointments are earlier than this it is only of academic interest. It is of more importance to ensure that a height first recorded at 0900, for example, is not remeasured on a subsequent occasion at 1100 or 1300, but as close as possible to the original time. Even half a centimetre represents a substantial proportion of a child's annual rate of growth and will make a significant contribution to the total error.

Once a child has been up for six or seven hours there appears to be no further discernible loss of height—the timing of afternoon appointments can therefore be more flexible and measurements made after 1300 can be repeated at any other time in the afternoon.

Though commonly used, the technique of stretching does not appear to have any advantages. It simply *increases* the measured height, in this case by almost 3 mm. This amount appears to remain constant, irrespective of the time of day at which the height is measured. Until recently, most growth charts recommended 'gentle upward pressure to the mastoid processes' to ensure that the 'maximum height' was recorded. In at least one revised version the maximum height has become the 'true height'. There is some confusion over this term; there can be no such thing as the 'true height' of an animate body, only a mean height, with variability about it. This mean height will be greater or smaller depending on whether the child is stretched or not. Greater, in this instance, does not mean better. The aim is not to record the maximum height possible, but a height that can be easily reproduced.

The amount of height lost between 0900 and 1500 was almost identical using stretched

(0.55 cm) and unstretched (0.56 cm) techniques. Stretching was therefore ineffective in reducing the stature lost during the course of the day, as suspected by Buckler.¹² Whitehouse *et al* had previously concluded that their new method had at least some effect in reducing diurnal variation.¹¹ They attributed their relatively small observed decrement (comparable with ours) to 'gentle upward pressure on the mastoid processes and verbal urging to reach upward'. Their children had also been up for a little while before the first measurement, however, and were therefore unlikely to shrink by the larger amounts reported by earlier observers. They also, crucially, did not include any unstretched measurements in their study. Had they done so, it might have been clear that, regardless of technique, only a small decrement was likely to be observed at that time of day.

This study confirms previous reports that measurements made by experienced observers using stretched and unstretched techniques are equally reproducible.^{4, 10} There is therefore no advantage of one method over the other in terms of the *precision* of the growth data obtained. Where there is a single experienced observer the method used is ultimately a matter of personal preference. Of more importance is the need to ensure the same method is used on subsequent occasions so that any increments observed in height are likely to be real and not attributable to differences in positioning or technique.

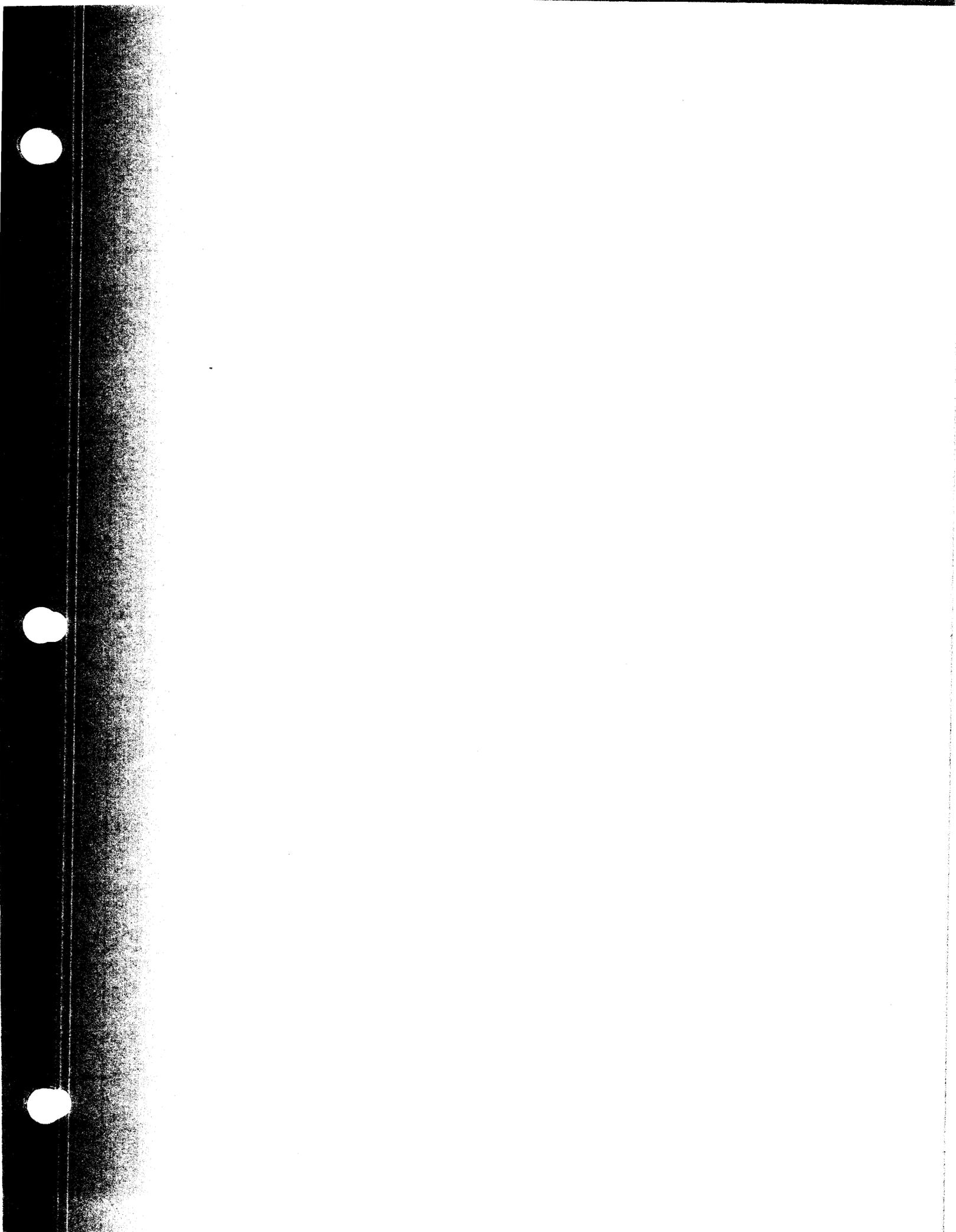
We have previously shown (though not on this occasion) that where stretching is used two observers, using ostensibly the same technique and the same instrument, can obtain significantly different mean heights for the same group of children.^{2, 4} Any difference in height obtained by two measurers over an interval of time is therefore likely to be due, in part, to the degree of stretching each observer uses. An unstretched technique removes this source of variability and is more easily reproduced from one measurer to another. There might therefore be a positive advantage in using this technique in situations where different observers will be monitoring the same child. Indeed, if universally adopted, differences between observers could be significantly reduced.

Conclusions

Diurnal variation in stature may substantially affect the reliability of height data and careful consideration should be given to the timing of repeat measurements. Even after a child has been up for two hours or so, further loss of height, amounting on average to half a centimetre, can be expected during the course of the morning. As little further loss of height is likely thereafter, growth clinics should, ideally, be held in the afternoon. The standard stretched technique does not appear to eliminate the effects of diurnal height loss, nor does it improve precision. Measurements made using an unstretched method are recommended to minimise interobserver error, known to occur where different observers are used.

We thank the pupils and staff of St Winifred's School, Southampton, for making this study possible. Grateful thanks are also due to Jean Mulligan, Pauline Mussen (PM), and Pat Tahmasaby for their assistance. LDV is supported by a grant to the Wessex Medical Trust from Pharmacia Upjohn.

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SPECIAL ARTICLE

Clinical longitudinal standards for height and height velocity for North American children

Longitudinally-based height and height velocity charts for North American children are presented. Centiles are given for early, middle, and late maturers. The shape of the curves is taken from a review of longitudinal studies, and the prepubertal and adult centiles for height attained are taken from National Center for Health Statistics data. The charts are suitable for following an individual child's progress during observation or treatment throughout the growth period, including puberty.

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IN 1956 Bayley^{1,2} produced charts for height and weight growth that, for the first time, took into account whether a child was an early or late developer. Her work derived from the classic studies of growth tempo by Boas^{3,4} (who coined that term) and by Shuttleworth.^{5,6} As standards, however, Bayley's charts lacked practicality, because they were based on very small numbers of subjects. Thus, although they indicated the average heights and height velocities to be expected in boys and girls maturing relatively early and relatively late, they did not give the population centiles

necessary in judging whether a child's growth is abnormal.

Ten years later, Tanner et al⁷ combined large-scale cross-sectional studies of a population (London County Council schoolchildren) with small-scale longitudinal studies (The Harpenden Growth Study and the International Children's Centre London Study) to produce longitudinal standards suitable for clinical use. These British-based height and height velocity and weight and weight velocity

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The three-color charts are available through Serono Inc., 280 Pond St., Randolph, MA 02368, or direct from Castlemead Publications, Swains Mill, 4A Crane Mead, Ware, Hertfordshire, SG12 9PY, England. They are printed in two formats: research (large) and clinic (A4 size).

NCHS	National Center for Health Statistics
PHV	Peak height velocity

charts have been widely used, and remain valid for the contemporary British population.⁸ In North America, however, children grow at a slightly faster tempo and are, on average, taller. There is a need, therefore, for clinical longitudinal standards for North America, based on the principles of the 1966 British Standards but using an American population survey and American data on growth tempo. We supply such standards for height and height velocity.

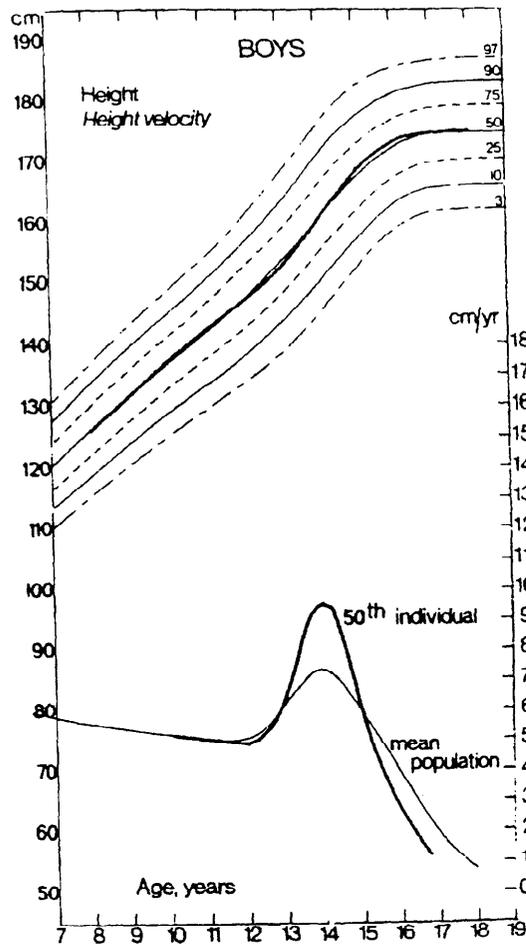


Fig. 1. Comparison of longitudinal individual and cross-sectional population standards. British longitudinal 50th centile individual curve (mean size, mean tempo) plotted (heavy line) on British population curves from London survey.⁸ Top, height attained; bottom, height velocity. (From Tanner JM: The uses and abuses of growth standards. In: Faulkner F, Tanner JM, eds: Human growth, ed 2. New York: Plenum, 1985, in press.)

These standards are an advance on the British standards in that the use of color printing enables them to carry more information. The British charts for height attained give simply the centiles characterizing the cohort of boys or girls with average growth tempo.¹⁰ Only in the height velocity charts are the centiles for early and late maturers also displayed. In the American height-attained charts, however, it has been possible to indicate not only the 50th centile for children with their pubertal growth spurts at the average time but also the 50th centile for children 2 SD of age early and 2 SD of age late. In addition, the 95th centile for height attained in a 2 SD early child and the 5th centile for height attained in a 2 SD late child are shown. Incidence of children on these centiles is about one in 1000 population.

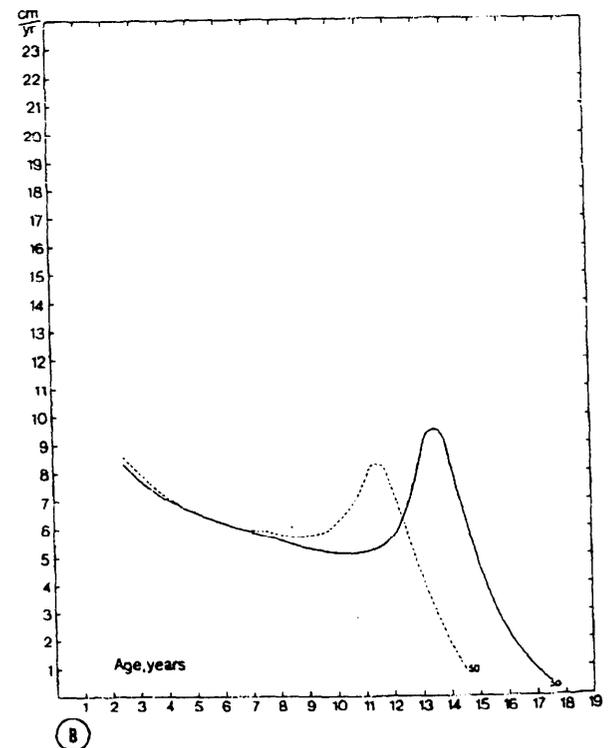
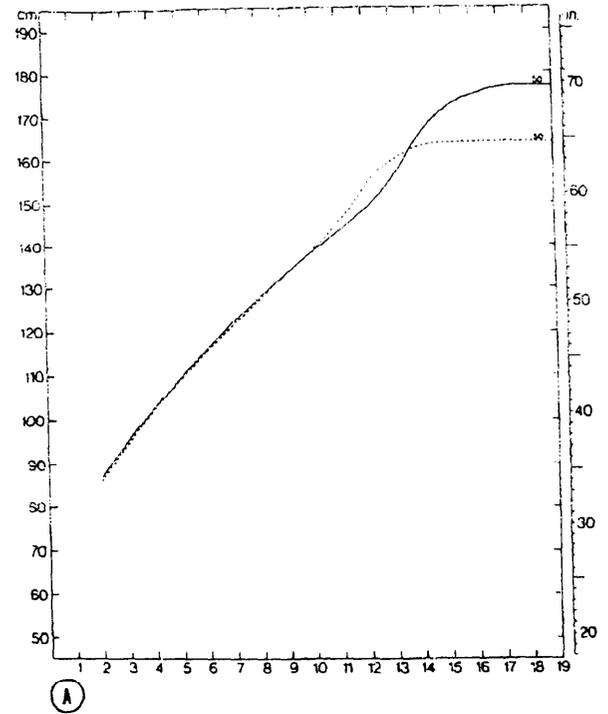


Fig. 2. The 50th centile curves for American boys (solid lines) and girls (dashed lines) of average growth tempo (that is, peak height velocity at average age). A, Height attained. B, Height velocity.

Table I. The 50th centile values for height and whole-year height velocity for boys and girls with peak height velocity at average times (13.5 and 11.5 years, respectively)

Age (yr)	Boys		Girls	
	Height (cm)	Height velocity (cm/yr)	Height (cm)	Height velocity (cm/yr)
2.0	87.0		86.0	
3.0	95.3	8.3	94.6	8.6
4.0	102.7	7.4	102.2	7.6
5.0	109.5	6.8	109.0	6.8
6.0	115.9	6.4	115.4	6.4
7.0	121.9	6.0	121.5	6.1
8.0	127.7	5.8	127.4	5.9
9.0	133.1	5.4	133.1	5.7
10.0	138.3	5.2	138.9	5.8
11.0	143.4	5.1	145.6	6.7
12.0	148.7	5.3	153.9	8.3
13.0	155.5	6.8	159.8	5.9
14.0	165.0	9.5	162.8	3.0
15.0	171.5	6.5	163.7	0.9
16.0	174.8	3.3	163.8	0.1
17.0	176.3	1.5		
18.0	176.8	0.5		

INAPPLICABILITY OF CROSS-SECTIONAL STANDARDS TO CHILDREN OLDER THAN 9 YEARS IN THE CLINICAL SETTING

There is much literature, stretching back to the nineteenth century, to point out the fallacy of using cross-sectional population curves such as those of the National Center for Health Statistics to follow the growth of individual children once puberty has begun.¹¹⁻¹³ The difficulty is that the 50th centile line derived from cross-sectional data is not actually followed by any individual child and is not the correct shape for a growth curve. This is most easily seen in terms of height velocity (Fig. 1, lower curves). The actual growth velocity in a child who is at the 50th centile for both size and tempo is compared with the curve of "velocity" obtained from the differences of successive cross-sectional population means. The pseudo-velocity curve has a peak that is at about the 3rd centile for

real individual peaks and is wider than any individual peak would be. Even in the height-attained, or "distance" formulation (Fig. 1, upper curves), although graphically the effect looks small, the cross-sectional means overestimate the 50th centile height of the average individual by 2 cm at age 13 years and underestimate it by 2 cm at age 15 years. These comparisons refer only to children with average growth tempo; in early and late maturers the discrepancy between longitudinal and cross-sectional standards is even greater. Thus there is a need for standards of the type that Boas, Shuttleworth, and Bayley recommended—standards that, in modern jargon, are said to be *conditional on tempo*.¹³

LONGITUDINAL STANDARDS

Average tempo child. The details of how the standards were constructed are given in the Appendix. It suffices to

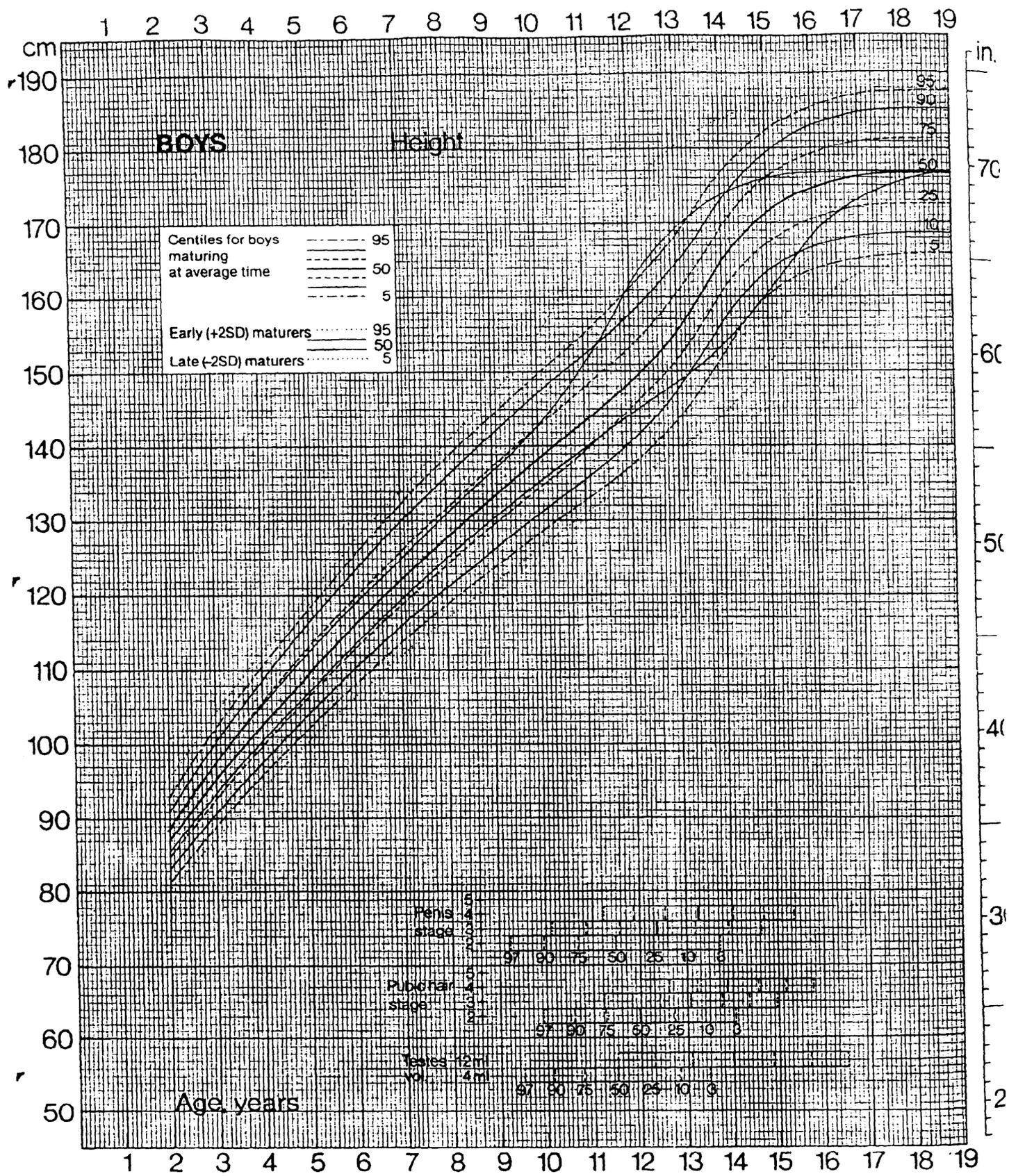


Fig. 3. Height attained for American boys. Red lines, 50th centile (solid) and 95th centile (dashed) for boys 2 SD of tempo early; green lines, 50th centile (solid) and 5th centile (dashed) for boys 2 SD of tempo late.

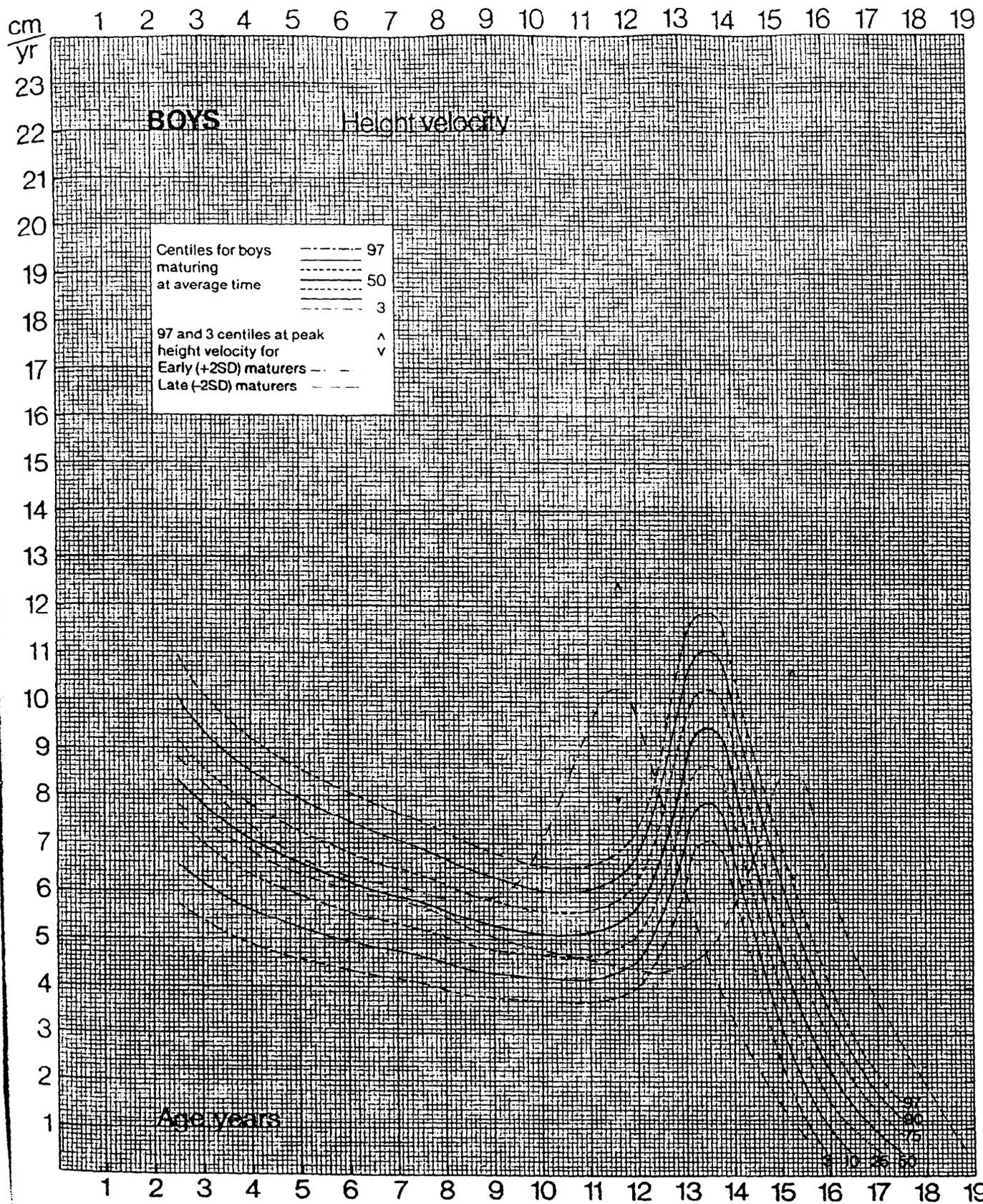


Fig. 4. Height velocity for American boys. Red line, 50th centile for boys 2 SD of tempo early; green line, 50th centile for boys 2 SD of tempo late. ^ and v, The 97th and 3rd centiles for peak velocities of early and late maturers, respectively.

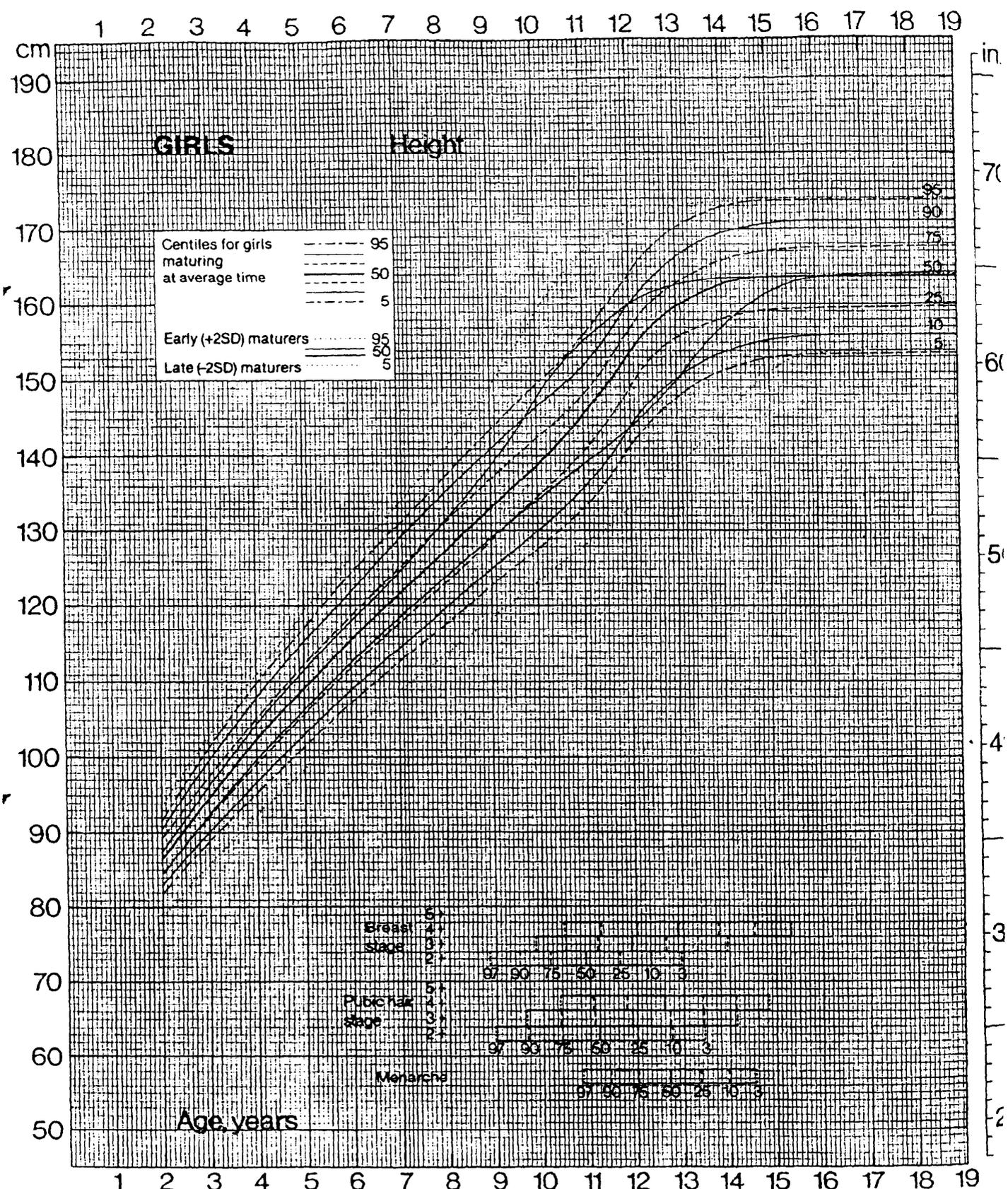


Fig. 5. Height attained for American girls. Red lines, 50th centile (solid) and 95th centile (dashed) for girls 2 SD of tempo early; green lines, 50th centile (solid) and 5th centile (dashed) for girls 2 SD of tempo late.

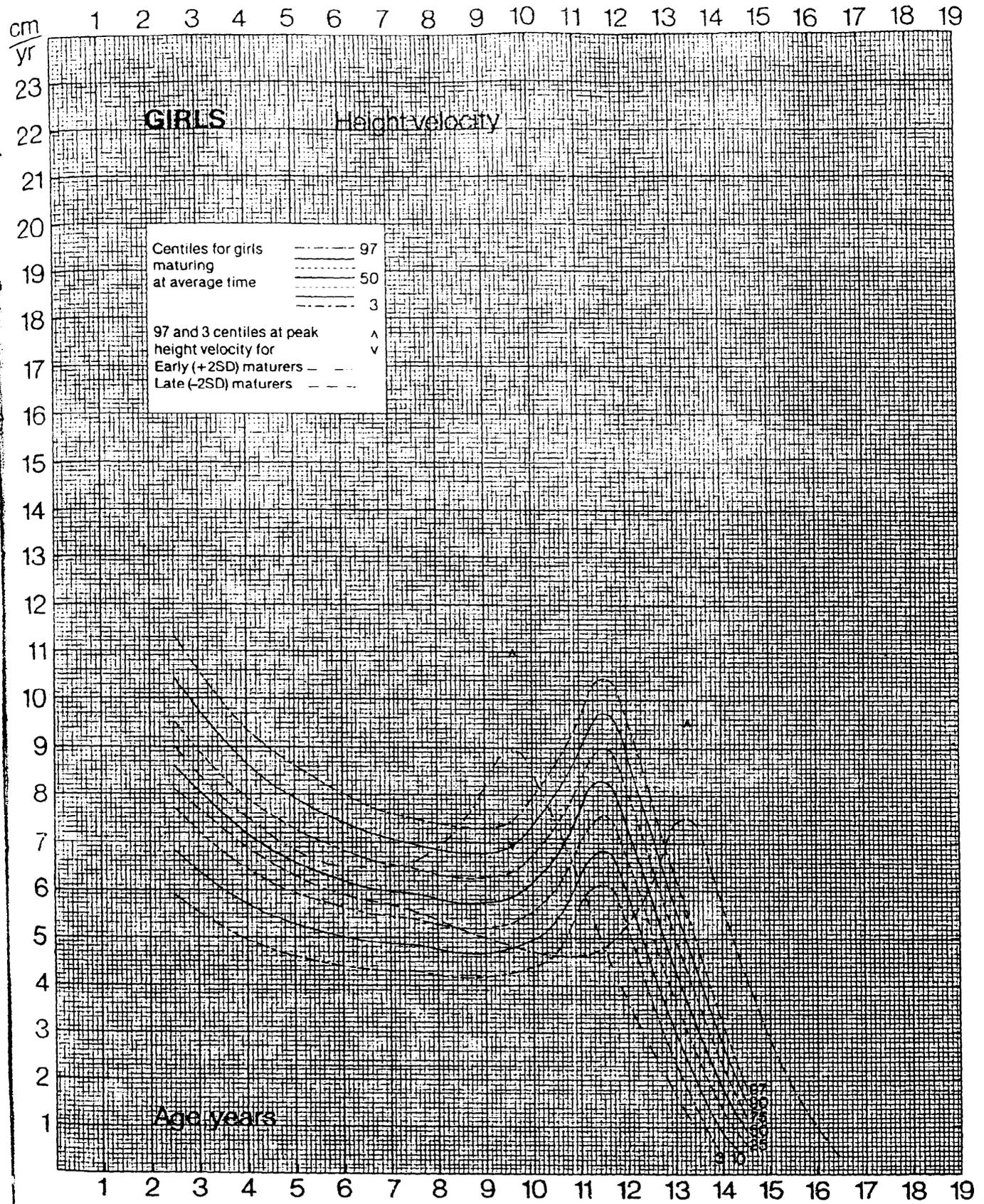


Fig. 6. Height velocity for American girls. Red line, 50th centile for girls 2 SD of tempo early, green line, 50th centile for girls 2 SD of tempo late. ^ and v, The 97th and 3rd centiles for peak velocities of early and late maturers, respectively.

Table II. The 50th centile height and height velocity values for boys and girls with peak height velocity 2 SD (1.8 yr) early and 2 SD (1.8 yr) late

Age (yr)	Boys				Girls			
	2 SD early		2 SD late		2 SD early		2 SD late	
	Height (cm)	Height velocity (cm/yr)						
2.0	88.4		85.6		87.6		84.4	
		8.8		7.8		9.0		8.1
3.0	97.2		93.4		96.6		92.5	
		7.8		7.1		7.9		7.3
4.0	105.0		100.5		104.5		99.8	
		7.0		6.6		7.2		6.5
5.0	112.0		107.1		111.7		106.3	
		6.5		6.2		6.6		6.1
6.0	118.5		113.3		118.3		112.4	
		6.2		5.9		6.5		5.8
7.0	124.7		119.2		124.8		118.2	
		6.0		5.7		6.6		5.6
8.0	130.7		124.9		131.4		123.8	
		5.8		5.2		7.4		5.2
9.0	136.5		130.1		138.8		129.0	
		6.2		4.9		8.9		4.9
10.0	142.7		135.0		147.7		133.9	
		8.2		4.7		7.4		4.7
11.0	150.9		139.7		155.1		138.6	
		10.3		4.5		4.9		4.8
12.0	161.2		144.2		160.0		143.4	
		8.0		4.3		2.7		6.1
13.0	169.2		148.5		162.7		149.5	
		4.5		4.8		0.9		7.3
14.0	173.7		153.3		163.6		156.8	
		2.3		6.9		0.1		4.4
15.0	176.0		160.2		163.7		161.2	
		0.8		8.1				2.0
16.0	176.8		168.3				163.2	
				4.7				0.5
17.0			173.0				163.7	
				2.8				
18.0			175.8					
				1.0				
19.0			176.8					

say that the 50th centiles for average tempo growth were based on the observed values of the NCHS from age 2 to 11 years in boys and from age 2 to 9 years in girls. Adult values (176.8 cm for men and 163.8 cm for women) were also taken from the NCHS data. From 11 years on in boys and 9 years on in girls, the height attained and height velocity curves have the shape characteristic of the growth of the typical individual. For reasons given in the Appendix, the age at peak velocity was taken as 13.5 years in boys and 11.5 years in girls, and the (whole-year) velocity at PHV as 9.5 cm/yr in boys and 8.3 cm/yr in girls.

These 50th centile curves, for the boy and girl of both

average height and average tempo, are illustrated in Fig. 2. The values for height and height velocity are given in Table I.

Early and late maturing children. We next determined the 50th centile curves for boys and girls who had their peak height velocities 2 SD of age early and 2 SD of age late. The SD of age at PHV is a little less than 1 year in nearly all published series; we have taken the value 0.9 years. The 2 SD early maturing boys therefore have average PHV at 11.7 years, the 2 SD late maturing at 15.3 years. The equivalent values for girls are 9.7 and 13.3 years, respectively.

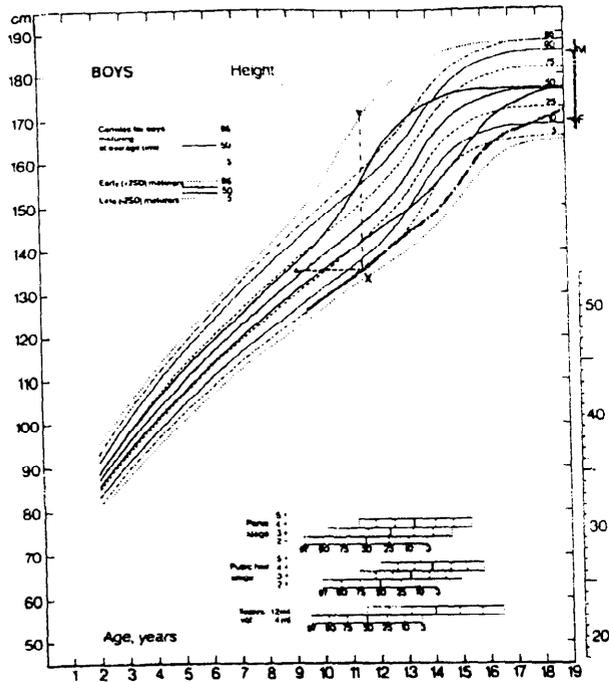


Fig. 7. Height curve of boy with constitutional growth delay. Bone age (Δ) and adult height prediction (\blacktriangledown) shown at age 11.6 years. *F* and *M*, father's and mother's height centiles; heavy vertical line, target height range. Height runs at about 15th centile for 2 SD late maturers until last point.

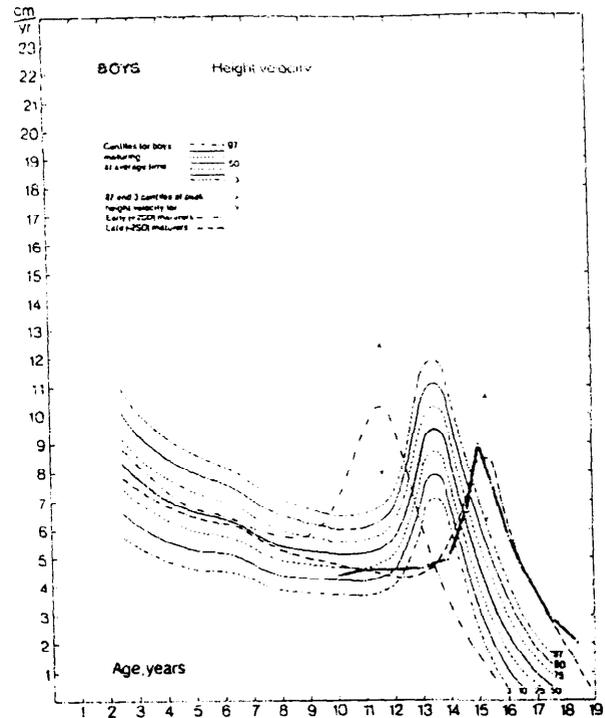


Fig. 8. Height velocity curve (same boy as in Fig. 7). Average curve for 2 SD late maturer is approximated throughout.

Although early and late maturing children on average attain the same adult height,¹⁴⁻¹⁶ their growth data begin to diverge quite early, the 2 SD early boys at age 5 years averaging about 5 cm taller than the 2 SD late boys; in girls the difference is about 5.5 cm. Early maturers have a higher PHV than do late maturers, and we have estimated the value of the 2 SD early peak at 10.3 cm/yr and the 2 SD late peak at 8.5 cm/yr in boys; the respective values are 9.0 and 7.6 cm/yr in girls (see Appendix).

The resulting curves are illustrated in Figs. 3 through 6; the values are given in Table II. Figs. 3 and 5, the suggested height attained standards, also give the 95th, 75th, 25th, 10th, and 5th centiles for the cohorts of average maturers. The adult and prepubertal values of these centiles (the latter slightly smoothed) are those of the NCHS. The NCHS gives the 5th and 95th as outside centiles, rather than the more usual 3rd and 97th, and we have retained this feature.

Also in Figs. 3 and 5, we give the 95th centiles for the cohorts of 2 SD early maturing boys and girls and the 5th centiles for the cohorts of 2 SD late maturing boys and

girls. The adult and prepubertal values were estimated on the basis of no relationship between tempo and final size, hence a similar SD of height in early and late maturers when fully grown, and also approximately before puberty. Because of this independence, these outside lines set limits outside which only $5\% \times 2.5\% = 0.125\%$, or about one in 1000 boys or girls, are situated. Intermediate centiles, both for tempo and for size at given tempo, can be readily approximated by eye, but are not included in Figs. 3 and 5 in order to avoid confusion.

Age standards for puberty stages¹⁴ are also given on these charts; by convention, 97th centile indicates early and 3rd centile late.

Figs. 4 and 6 give the velocity standards for boys and girls. The centiles (outside limits 97th and 3rd centiles) are those for the median tempo cohorts; also given are the 50th centiles for the 2 SD early and 2 SD late cohorts, with accents (∇ and \blacktriangle) at 97th and 3rd centile peaks for the accompanying centiles.

Strictly speaking, these charts refer to *whole-year* velocities converted from increments that should be taken over not less than 0.85 years and not more than 1.15 years. Velocities calculated over shorter periods reflect seasonal

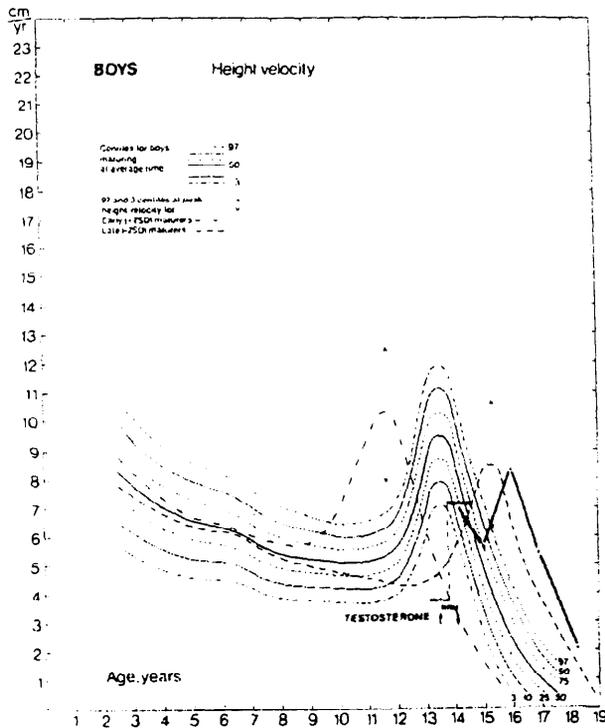


Fig. 9. Height velocity curve for boy with constitutional growth delay treated for 6 months with low doses of testosterone (50 mg enanthate each month).

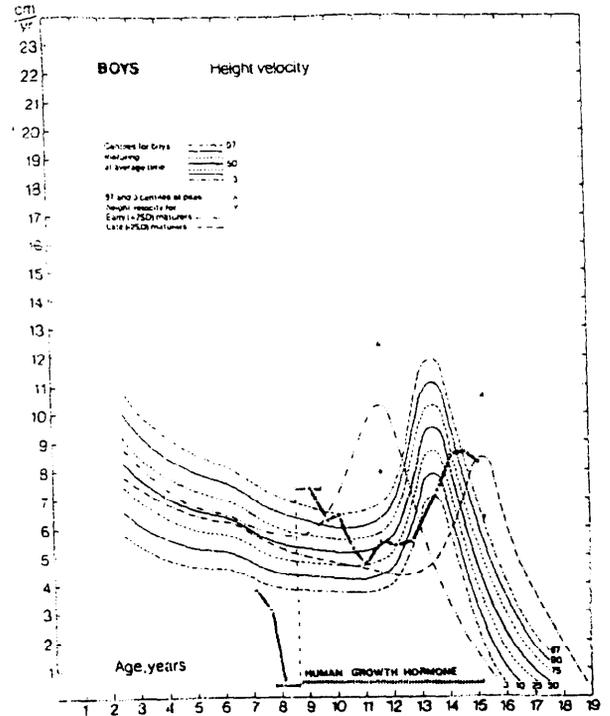


Fig. 11. Height velocity curve (same boy as in Fig. 10).

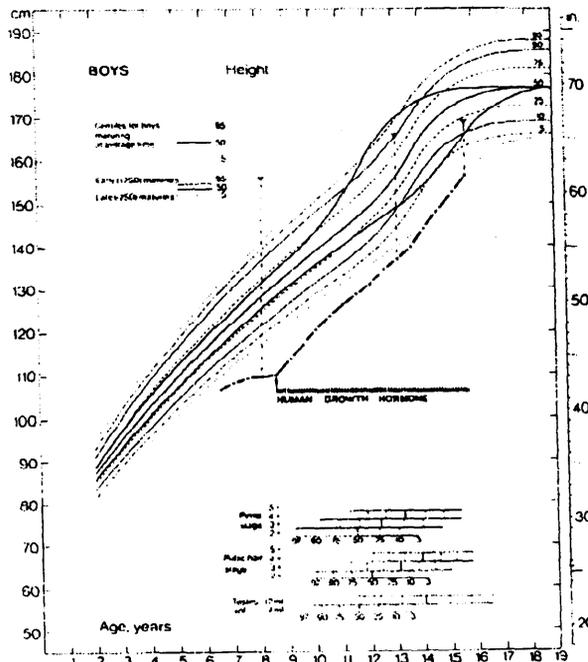


Fig. 10. Height curve of boy with growth hormone deficiency, treated with human growth hormone (15 IU/wk). Adult height predictions at three ages are illustrated.

effects (most children grow faster in the spring and slower in the fall) and are relatively more affected by the unavoidable errors in measurement (which should not exceed 3 mm). Hence, for 6-month periods, rate rounded to centimeters per year, the centiles are wider; roughly speaking the 6-month 90th and 10th centiles are located at the 1-year 97th and 3rd centiles.

Use of charts. We give two examples of the use of the charts. In the first example, constitutional growth delay is followed in two boys, one without medication and the other given short-term low-dose testosterone. In the second, the effect of human growth hormone on the growth of a boy with growth hormone deficiency is charted.

Figs. 7 and 8 show the height and the height velocity in a boy with growth delay first seen at age 9.6 years. Bone age¹⁷ is plotted as shown for the visit at 11.6 years; the length of the horizontal line gives the retardation in years, and the plot (Δ) itself displays the height for bone age. Adult height prediction¹⁸ is plotted at the termination of the vertical line erected at x. These two determinations were, of course, repeated at intervals during the ensuing years, but further points are omitted in the interests of clarity. Also indicated are parental height centiles (mother's height plus 13 cm) and the target height for the child, that is, the range of heights within which 95% of sons of these parents should fall as adults (average of father's and

mother's centiles ± 10 cm).¹² The whole-year velocities follow the 2 SD late maturing curve quite closely (Fig. 8). (During 6-month visits they are calculated each time for the whole preceding year.) Velocities are plotted at the center point of the period covered.

In this patient only reassurance was given, based specifically on the charts, which were explained to the boy and his parents. Bone age, adult height prediction, and target height are the key elements, together with the ability of the pediatrician to say exactly how much growth will occur in the next year, the year following, and so on. When parents of a 13-year-old boy complain that he has not grown for the last year or so, they can be reassured, on these bases, that the adolescent spurt is about to begin, that growth next year will be about 6 cm, and the year after that 8 or 9 cm. Often such reassurance suffices. In Fig. 9 is shown the growth curve for a boy given testosterone enanthate, with a careful check on the change in height prediction. The effects of such treatment are best followed in the velocity chart. In this particular boy the treatment was discontinued after 6 months, and the growth velocity fell until the normal pubertal growth spurt (in this instance the rule of whole-year plotting cannot but be broken, with suitable caution in interpreting velocity). When a treatment has been initiated at the beginning of a period, we thicken the vertical line joining the two periods, rather than joining up the adjacent velocities as we did in Fig. 8.

In Figs. 10 and 11 the effect of human growth hormone is shown. The catch-up growth (or velocity above that normal for age) is well seen in the first few years. The steadily increasing prediction of adult height is indicated by the three illustrative occasions plotted.

Examples of many such plots for both normal and abnormal children will be found in Tanner and Whitehouse.¹⁹

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Appendix

CONSTRUCTION OF 50TH CENTILE CURVE FOR AVERAGE TEMPO

Boys. From ages 2.0 to 11.0 years, the values for height follow the observed NCHS 50th centiles of Hamill et al.¹ (Table 6, p 28), slightly smoothed graphically to fit with the shape of the height velocity curve, which takes into account the slight decrease in deceleration occasioned by the mid-growth spurt.^{2,4} Values taken for 1-year velocities at ages 5 to 6, 6 to 7, and 7 to 8 years had regard to the observed NCHS cross-sectional mean differences, the actual mean annual increments seen in the large-scale London County Council 1-year longitudinal study of Tanner and Cameron,² and the increments seen in the small-scale longitudinal studies of Largo et al.³ and Karlberg et al.⁶ (p 7). In every yearly point, our smoothing fits the observed values of the NCHS better than (7 points) or as well as (3 points) the smoothing procedure adopted by Hamill (Table 13, p 37). At 11.0 years the observed NCHS value was 143.5 cm, our value 143.4 cm.

From 11.0 years on, we grafted the NCHS values for prepuber-

tal height, adult height, and age at peak height velocity onto the shape of the height and height velocity curves that characterize the growth of the typical individual. The adult value was taken as 176.8 cm (Table 13, p 37, in agreement with the estimate derived by fitting a Preece-Baines⁸ model I curve to the observed values of the NCHS). The age at PHV is approximately 13.5 years if taken from the observed cross-sectional semiannual values of the NCHS (Table 6, p 28), and 13.4 if estimated by fitting a Preece-Baines curve to the observed cross-sectional means. (The smoothed NCHS values, given as Table 13, practically obliterate any pubertal rise and lead to a clearly erroneous age at PHV of about 12.8 years; they are best ignored.) A value of 13.5 years for age at PHV is 0.4 years lower than the age at PHV of the British standards, and agrees well with calculations for girls (see below) and with the differences in bone ages between the two populations.⁹

We also needed a value for PHV itself (not instantaneous PHV, but peak velocity computed over a whole year, because the velocity standards are presented this way). There were a number of empirically determined values, all in fair agreement. Tanner et al.¹⁰ fitted measurements taken every 3 months on each individual by an iterative graphic procedure, starting with the height-attained curve, then plotting the observed velocities against the estimated velocities, smoothing and repeating the cycle a second time. Their mean whole-year PHV was 9.5 cm/yr. Using similar graphic procedures, also on 3-month measurements, Taranger et al.¹¹ found a mean of 9.9 cm/yr in the Stockholm Longitudinal Study. Lindgren¹² estimated a mean of 9.8 cm/yr in the all-Sweden twin longitudinal study, using 373 singleton (control) boys measured every 6 months. Billewicz et al.¹³ obtained a mean of 9.6 cm/yr in 669 boys in Newcastle-upon-Tyne examined at 6-month intervals, but this is the maximum 6-monthly peak velocity and corresponds to about 9.3 cm/yr for the whole-year peak velocity.

Largo et al.⁵ fitted cubic splines to 6-monthly height values of boys in the Zurich longitudinal study and found a mean PHV of 9.0 cm/yr. Authors who have fitted parametric curves have found lower values still; for the Berkeley growth study data reported by Tuddenham and Snyder,¹⁴ the Preece-Baines model I curve gives a mean of 8.4 cm/yr (our calculations), and the triple logistic curve a mean of 8.7 cm/yr¹⁵; these values are for instantaneous peak velocity, which is greater than whole-year peak velocity by approximately 0.8 cm/yr in boys and 0.6 cm/yr in girls.¹⁰ The graphically fitted whole-year peak velocity in these data comes out to 8.9 cm/yr, 1.3 cm above the whole-year peak estimated by the Preece-Baines method (which is 8.4 - 0.8 cm/yr). Thus it seems that parametric curves at present are insufficiently flexible to accommodate the full rise of the observed curves. The Preece-Baines curve, for example, when fitted to the British male standards, underestimates PHV by 1.5 cm/yr. Similarly, when fitted to a subsample of the Tanner¹⁰ data, it produced a value of 8.7 cm/yr compared with the graphic instantaneous value of 10.3 cm/yr. We have relied, therefore, on the empirically derived values, and chosen the midrange figure of 9.5 cm/yr.

Girls. Exactly similar considerations for girls led to the 50th centile curves shown in Fig. 2 and the values given in Table 1. For the prepubertal value, at age 9.0 years, we have taken 133.0, the

NCHS observed value at this age being 132.7. Our values fit the observed NCHS means better than do the spline-smoothed NCHS values in four of seven cases. For adult height we have taken 163.8, the NCHS observed value being 163.7. We located PHV at 11.5 years, which was the same from the observed NCHS values, the Preece-Baines fit to them, and the NCHS cubic spline fit. This value is confirmed by considering the average difference in time between age at menarche and age at PHV, which is between 1.2 and 1.3 years in nearly all published series. The NCHS value for menarche is 12.77 years.¹⁶

Whole-year PHV values in the empirically derived data are 8.4,¹⁰ 8.6,¹¹ and 8.3 cm/yr.¹² There are 6-monthly PHV of 8.0 cm/yr, leading to about 7.8 cm/yr for whole-year for Newcastle,¹¹ and 8.3 cm/yr, leading to about 8.1 cm/yr for whole-year in the Polish longitudinal study reported by Bielicki.¹⁷ Cubic splines fitted to the Swiss data give a value of 7.1 cm/yr,⁵ and Preece-Baines model I curves give instantaneous values of 7.3 cm/yr¹⁴ (Belgians), 7.8 cm/yr¹⁹ (Americans), 7.4 cm/yr (Berkeley Growth Study, our calculations), and 7.7 cm/yr (Harvard School of Public Health Growth Study, our calculations). We have taken the value 8.3 cm/yr.

Early and late maturing children. Values for the difference in height between 2 SD early and 2 SD late boys at age 5 years were derived from the regressions of height at age 5 years on age at PHV, which, using fitted Preece-Baines curves, were -1.1 ± 0.5 cm/yr in the Berkeley data and -1.8 ± 0.4 cm/yr in the Harvard data. For girls the regressions were -1.3 ± 0.6 cm/yr (Berkeley) and -1.9 ± 0.5 cm/yr (Harvard).

The regression of PHV on age at PHV, in boys, in the data of Tanner et al.¹⁰ was -0.8 cm/yr; in the Newcastle data -0.4 cm/yr,¹² in the Polish data approximately -0.6 cm/yr,¹⁷ in the Swedish data -0.5 cm/yr,²⁰ in the Harvard Growth Study -0.5 cm/yr,²¹ and in the Swiss data, using spline fits, -0.5 cm/yr.⁵ In the Berkeley data it was -0.6 ± 0.1 cm/yr, and in the Harvard School of Public Health data -0.4 ± 0.2 cm/yr, both using Preece-Baines fits. We have taken -0.5 cm/yr as the value, giving the 50th centile PHV for 2 SD early maturing boys as $9.4 + 0.9 = 10.3$ cm/yr and for 2 SD late maturing boys as $9.4 - 0.9 = 8.5$ cm/yr.

In girls the regression is a little lower than in boys. Estimates are -0.5 cm/yr (Tanner et al.¹⁰), -0.4 cm/yr¹³ (Newcastle), -0.4 cm/yr¹⁷ (Poland), -0.3 cm/yr²⁰ (Sweden), -0.5 cm/yr²¹ (Harvard Growth Study), -0.4 cm/yr⁵ (Swiss children, spline fitted), -0.6 cm/yr (Berkeley data, fitted Preece-Baines curves), -0.4 cm/yr (Harvard School of Public Health, fitted Preece-Baines curves), and -0.1 cm/yr¹⁸ (New England, fitted Preece-Baines curves, but home measured and with very high SD for PHV). We have taken the value -0.4 cm/yr, giving 50th centile PHVs of 9.0 cm/yr for 2 SD early maturing and 7.6 cm/yr for 2 SD late maturing girls.

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DESIGN AND ANALYSIS OF STUDIES TO ASSESS THE EFFECT OF INHALED CORTICOSTEROIDS ON GROWTH

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Assessment of child growth is problematic: growth is nonlinear in the long-term, and unpredictable in the short-term; growth is subject to a number of environmental as well as genetic influences; and growth is difficult to measure reliably. The potential for growth delay as an effect of asthma is established, although it has proved difficult to quantify how great an impact this has on height, growth velocity, or final attained height. In the treatment of asthmatic children, there remain uncertainties as to the effect of inhaled corticosteroids on growth, given the great number of factors affecting growth. In this paper we present recommendations for the design and analysis of trials to assess the effect of regular treatment with inhaled corticosteroids on growth in asthmatic children. Design recommendations are articulated for study duration, entry criteria, other factors that may affect growth, measuring height, measuring growth, study objectives, and considerations relating to confounding between treatment allocation and the effect of the disease on growth. Special attention is given to analyses that address both the intra-subject correlation arising from multiple measurements in longitudinal studies of growth and the potential bias in treatment comparisons due to dropouts, especially those due to treatment failure.

Key Words: Growth; Study design; Statistical analysis; Mixed model; Inhaled corticosteroids; Asthma

INTRODUCTION

CHILDHOOD GROWTH IN asthmatics is a complex process and is influenced by a number of factors (1-5). Corticosteroids are

an effective means of treating asthma. It has long been known, however, that oral corticosteroids have a systemic effect (1,6,7) and can reduce growth when used for short periods or over prolonged periods of time. Inhaled corticosteroids treat the airways topically in the lungs and are the recommended therapy for long-term control of asthma in children with moderate and severe disease,

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as well as one of the therapeutic options for children with mild persistent disease (8).

In clinical trials evaluating growth in asthmatic children, estimating the extent to which inhaled corticosteroids have an effect on growth has been confounded by factors such as puberty and withdrawal from the study due to the underlying disease. Asthma itself may affect growth, especially if uncontrolled (1,3,9,10,11). Trial designs usually do not account for subjects who discontinue due to asthma exacerbations, a marker of poorly controlled disease. This can result in a differential dropout rate between treatment arms, particularly in placebo-controlled trials, and is indicative of the possibility that differing amounts of asthma control between treatment arms may allow for different effects on growth from the disease itself. The exact mechanism(s) by which asthma affects growth and how much impact varying asthma control have on the disease are unknown. In addition, growth per se is difficult to measure due to diurnal variation in height (12), seasonal variation in growth rates (13), and differing techniques and equipment for measuring height (14).

In July 1998, the Food and Drug Administration (FDA) convened a joint pulmonary and endocrinology advisory committee meeting on this topic. FDA speakers reviewed the literature and five sponsor studies, and interpreted the evidence to conclude that all inhaled corticosteroids may affect child growth. The issue of confounding between treatment arm and nonrandom dropouts was mentioned as a design issue during this meeting (15) and needs to be considered in the interpretation of results.

One recommendation of the advisory committee was that clinical programs for new inhaled and intranasal corticosteroid drug products include a growth study. Subsequent to the recommendation, FDA has indicated that there will be a draft guidance issued on how to design such studies. An early indication is that this guidance document will address the issues associated with confounding (16). We will return to this in the discussion section.

It is essential to have a well-designed trial in which an accurate assessment of growth is obtained and where key factors that may impact upon growth are collected. Presented first are general recommendations for the study of growth, followed by more specific recommendations for the study of inhaled corticosteroids in asthmatics.

STUDY DESIGN

Study Duration

While it is recognized that final adult height is the most important growth measure (17), it is not possible to obtain such information until a product has been on the market for a number of years and children have had the occasion for long-term exposure.

The next best option for new drug products is to assess changes in height over a specified time period. Too short a treatment period is likely to lessen the value of the data as an indicator of the effect on long-term growth (1). Longer treatment durations are more problematic from the viewpoint of consistency in drug administration and subject loss to follow-up. We believe that a 12-month treatment duration represents an appropriate balance.

Inclusion of a six-month run-in period to assess prestudy growth velocity and a follow-up time period to assess catch up growth are considerations FDA favors (15). Interpretation of such results will be dependent on the extent to which oral and inhaled corticosteroids are used during these time periods.

Entry Criteria

To avoid confounding with concomitant growth disorders, it is essential to recruit subjects of normal height, weight, and growth rate. This can be done by comparing the height, weight, and growth rate of each child against relevant standard norms, and excluding those children at the extreme percentiles. Subjects with known growth disorders or who are taking medication likely to affect growth should be excluded from the study.

It is also important to consider the ages of children. Puberty is a period of erratic and unpredictable growth, and hence has the potential for confounding with treatment arm. It is, therefore, advisable to exclude children of an age who could enter puberty during the course of the study (3). The Tanner rating of sexual maturity (18) should also be performed throughout the course of the study and only subjects remaining prepubertal at the end of the study should be included in the primary analysis.

Data Collection of Factors That May Affect Growth

In addition to regular measurements of height throughout the course of the study, a review of the literature has shown that the following factors are considered important in affecting growth and should, therefore, be assessed and accounted for in the analysis. Age, gender, ethnic origin, and previous corticosteroid usage are commonly used in modeling growth. In addition, age at onset of wheezing (19), socio-economic status (4), and exposure to smoking (20) have been demonstrated to affect growth and should be assessed and adjusted for via inclusion in an appropriate statistical model.

Measuring Height

The review at the advisory meeting in July 1998 of published growth studies using inhaled and intranasal corticosteroids found that the magnitude of the effect on growth velocity ranged from 0.5 to 1.5 cm/year (15). Accurate measurement of height to the nearest millimeter on good quality equipment is essential in order to detect small treatment differences. The following procedure for collection of height data needs to be utilized in clinical trials:

- Standardized stadiometer across sites, calibrated prior to each measurement (14),
- Same person responsible for measuring a subject throughout the study (12,14),
- Measurements taken at same time of day

throughout the study for a subject, preferably in the afternoon (12),

- Measurements performed in triplicate at each timepoint, and
- Detail other standard procedures (14) for example, bare feet, hair worn down, unstretched (12), and horizontal position of head.

Measuring Growth

There are two alternative methods for measuring growth over time:

- Growth velocity (cm/yr), and
- Standard deviation (SD) scores, referencing actual growth velocity to a suitable normal growth rate standard.

SD scores are calculated as:

$$\text{SD Score} = \frac{(\text{subject GV} - \text{normal GV})}{\text{normal GV standard deviation}},$$

where GV is growth velocity and 'normal' is with respect to the normal reference for the same age and gender (21).

Measures such as height (cm) or SD scores based on height do not address growth. Assessment of height alone after a period of treatment may allow one to evaluate differences between treatments (22), but it is much less sensitive than height over time. To demonstrate, consider a 6-year-old boy with normal height (116 cm) at the 50th percentile using commonly available growth velocity norms (13). After a year on a hypothetical growth study, assume that his height changed by 4, 5, or 6 cm, as noted in Table 1. If only his height information were available, we would be unlikely to conclude that there was a growth effect, since even growth of 4 cm yields a height value of approximately 28th percentile. However, taking into account the baseline information, a more sensitive interpretation can be made. This growth rate of 4 cm/yr yields a growth velocity value of less than the 3rd percentile.

There are advantages to analysis of SD

TABLE 1
Hypothetical Results for a 6-year-old
Male on a Year-long Growth Study

Height (cm)	Change (cm/yr)	Height Percentile	Growth Velocity Percentile
122	6	50	50
121	5	~35	~12
120	4	~28	<3

scores and advantages to the direct measure in cm/yr. The benefits of analyzing growth velocity (cm/yr) include ease of interpretation and direct applicability to clinical practice. Growth velocity, however, does not account for subject age and gender, which are important factors in assessing normal growth. If the subject population is in an age range where normal growth velocity is approximately linear, and the effect of age on growth rate has only linear (and quadratic) components, this may still be accounted for by inclusion of age (and age squared) and gender in a statistical model.

SD scores have the advantage of standardizing across age and gender, which allow for a more direct comparison of treatment group differences over the age and gender profile of the population under study. SD scores are more advantageous when growth rates are not linear across the age range being studied. Because of the nonlinear nature of growth during puberty and early childhood, it is anticipated that SD scores may better account for these variations in age and gender in comparison to inclusion of age and gender in the statistical model.

It should be noted that reference data for calculating SD scores might be out-of-date or nonexistent for some countries and/or ages. There are also concerns about the accuracy of these charts due to their distributional assumptions, their methods of smoothing, and the use of cross-sectional rather than longitudinal data. More significantly, however, asthmatics do not grow at the same rate as normal children and thus the reference group will not provide an appropriate comparison. This

is especially important in studies without a control group (23), since comparison of a single-armed study to normal children will confound growth reduction due to the drug with growth reduction due to the disease.

Another method to incorporate information about growth from normal populations is to use percentiles from normal growth curves. As with SD scores, age and gender effects are inherently taken into account. These percentiles are difficult to obtain, however, as they require interpolation from growth curves. A simpler way to summarize the data is using a contingency table, categorizing across treatment groups by frequency of subjects below the third percentile, tenth percentile, and so forth, at the beginning and end of the trial. This method allows one to identify those subjects who may be particularly susceptible to corticosteroid treatment. It does not, however, delineate between those slightly below a cut-off and those greatly below it (21). Perhaps a more sensitive method to investigate these susceptible subjects would be to define a cut-off based on SD scores or cm/yr. SD scores utilize the same external information as percentiles if, as in the case of Tanner and Davies (13), percentiles are simply calculated by assuming normality and incrementing multiples of the standard deviation from the median.

Study Objectives

The objective with respect to growth will depend upon whether the study is designed to compare against another inhaled corticosteroid (active or positive control), or against a control not anticipated to have growth effects (negative control). In the case of comparing to a negative control, the objective may be to demonstrate equivalence (or non-inferiority) or to estimate size of effect. In the case of comparing to another corticosteroid, superiority will be the objective if the product is expected to have less effect on growth than the control (24,25).

Ideally, study objectives should not focus on the side effects of the drug without regard to the effects of the disease itself. A different

objective could be to answer the question "What information does the prescribing physician need in order to assess what is best for a patient?" To answer this question, studies that compare the growth effects in children on a given inhaled corticosteroid with other children on clinically appropriate interventions should be considered. For example, some children in a negative control arm might occasionally need an oral steroid burst to keep their asthma controlled. This kind of comparison would assess whether long-term use of inhaled corticosteroids, where a consistently high level of asthma control is anticipated, is better than short-term use of oral corticosteroids with variable asthma control: inhaled corticosteroid treatment causes minimal effect on growth while providing adequate control of the disease. Consideration should also be given to a design that incorporates titration to the lowest effective dose, thus further improving the risk/benefit ratio.

Confounding with Treatment Arm

Previous growth studies have highlighted a key confounding factor in the analysis of growth. In studies with a placebo control, withdrawal due to worsening asthma has been confounded with treatment allocation. Given that asthma control is likely to be inferior for subjects in the control arm, it is likely that a differential dropout rate will occur. The more severely ill subjects will withdraw from the control arm, leaving the milder, potentially faster growing subjects. In the corticosteroid arm, however, both mild (faster growing) and more severe (slower growing) subjects are likely to remain. If this factor is not taken into consideration, an apparent difference in growth rates between treatments may be wrongly attributed to the corticosteroid.

There is no simple solution to this problem. For subjects withdrawing after four to six months of treatment, we are still able to obtain a reasonable estimate of annual growth velocity. For the less controlled subjects who withdraw during the first four to six

months of treatment, however, an estimate of annual growth velocity is likely to be distorted due to the nature of how children grow (1,26,27). Our recommendation is to collect height data after treatment failure for these subjects. This option is not ideal, as these subjects are likely to be given a medication (prednisone burst or another inhaled corticosteroid) that also has potential to impact growth. Some information can still be salvaged, but the resulting comparison may be of treatment strategies, rather than comparison to a negative control.

Consideration should also be given to the use (where appropriate for the dose) of only mild persistent asthmatics (16), since recommendations for long-term control in this group include low dose corticosteroid, nedocromil, or cromolyn (8). Characterization of only mild persistent asthmatics via entry criteria may be difficult to achieve, however, and conclusions for more severe asthmatics cannot be drawn directly from the study of mild asthmatics. Although the nonrandom dropout phenomenon should be diminished in this milder group, measures should still be taken to assess whether it occurred and to manage the issue through suitable design.

The relationship between asthma, uncontrolled asthma, and growth is a complex one that is not well understood. If ethically feasible, a 2×2 factorial design comparing normals and asthmatics with and without inhaled steroid treatment could be considered to examine the absolute effects of steroids on growth. Such a design, however, assumes incorrectly that the effect of asthma/asthma control is constant across subjects. In addition, there is evidence (28) that normal children would get larger doses of drug due to greater peripheral lung deposition, and so the impact on normal children is also irrelevant because they would presumably receive a higher systemic dose than their asthmatic counterparts.

Age is also a potential confounding factor. For example, if the age range of children included in the study spans very different growth curves (such as children 1–2 years old and 2–4 years old) implying that growth

is not easily modeled across this age range, then a stratified randomization would be preferred.

STUDY ANALYSIS

Several possible analyses are presented in this section for studies of growth in prepubescent asthmatic populations. It is important to note that any growth effects due to asthma are confounded with growth effects due to treatment because nonasthmatic children are not enrolled in these studies. Also note, it is assumed that growth rate is linear for the time period studied.

The main purpose of this section is to consider the confounding of treatment arm with dropouts due to lack of efficacy. Methods for handling this situation are separated into three cases. The first case assumes dropouts are missing completely at random (MCAR) or MCAR within treatment groups as described by Little and Rubin (29). MCAR within treatment groups implies that within a given treatment group the probability of withdrawal is the same for every subject regardless of the value of his/her response. In the second case, methods will be considered under the assumption of missing at random (MAR) (29). The MAR mechanism implies that the probability that a given patient will drop out may depend on past observations but not on potential current or future observations. The third case to be considered is that dropouts are neither MCAR nor MAR.

The analyses presented here will assume the following setting. Prepubescent children meeting inclusion criteria are randomly assigned to treatment groups. Age, gender, baseline height, and growth rate are collected, and subject heights are measured at several periodic intervals through the course of the study. Other covariates such as ethnicity and socio-economic status may also be assessed at entry and included in the model.

Assuming Dropouts are Missing Completely at Random (MCAR)

MCAR may be a reasonable assumption in studies comparing the effects of two different inhaled corticosteroids on growth or in a

study of intranasal corticosteroids for rhinitis. If the design considerations given in the previous section are employed, it is less likely that the dropout rate would be confounded with treatment arm, dropout rates would be small, and the effect of any nonrandom dropouts on treatment comparisons would be minimal. All of the analyses presented here give unbiased estimates under the MCAR assumption.

With multiple observations per subject taken over time, the data in their raw form do not possess the statistical property of independence. Hence, approaches to these data must either consider the within-subject dependence in the analysis or reduce the data to one observation per subject. Possibilities for reducing the data to one observation per subject include estimating the growth rate using only the first and last observation (described hereafter as the two-points approach) and using all the observations to estimate the growth rate by fitting a line to the height observations from each subject (described hereafter as the slope approach). The slope approach differs from the two-points approach in that it uses all the available information and is more robust to the variability of growth rates observed due to measurement error. With either approach under the MCAR assumption, it is reasonable to require a subject's observations to span some minimum amount of time (eg, 4 or 6 months) to ensure a reasonable estimate. Reducing multivariate data to univariate data has been used in similar settings (30) and is discussed in more general terms in Ghosh et al. (31).

Once the data have been reduced to one observation per subject, several possibilities for analysis exist. One tactic is to model the growth rates directly using a general linear model (GLM). In the example below, growth rate is regressed on treatment, gender, investigator, baseline rate, age, age², and age by gender interaction. Age² is included in the model to capture the slight curvature of growth curves that is apparent in prepubescent children. The age by gender interaction is included because the difference between male and female growth rate curves depends

on age. Other covariates believed to affect growth should be included if available.

With the slope approach, subjects who did not complete the study can still have a regression line fit to their observed heights provided that at least two observations are available. In addition to estimating the slope, the variance of the slope estimate can also be obtained provided three or more points are available. Subjects can then be included in the model using slope as the response variable in either a weighted or unweighted manner. Using the inverse of the variances of the slopes as weights provides asymptotically best linear unbiased estimates when dropouts are MCAR. The advantage of using weights is that slopes that are less precisely estimated from fewer observations are not given undue influence. However, since subjects with fewer observations are generally not given the weight they would have, had they completed the study, using weights may introduce additional bias when dropouts are not MCAR. For this reason the weighted GLM approach is only recommended under the assumption of MCAR.

Other options for analysis involve using growth curves such as those of Tanner and Davies (13) to obtain SD scores. These SD scores can then be modelled in the same manner as above without having to include age, gender, age², or age by gender in the model. Disadvantages and advantages of this strategy have been discussed above.

An alternative to reducing the data to one observation per subject is to use all the observations, that is, all height measurements taken on each subject, with a mixed model approach (with subject being treated as a random effect). Here, the pattern of dependence of observations within each subject is modelled uniformly across subjects. An AR(1) plus compound symmetry dependence structure (32) is assumed for the analysis presented below in the results section. This means that all observations on the same subject are considered to be correlated to at least some degree, but pairs of observations closer together in time are considered to be more correlated than pairs farther apart. REstricted

Maximum Likelihood (REML) is used to estimate regression parameters and variance components. Some brief details of this approach along with SAS (33) code are given in the Appendix. This approach potentially has more power than the univariate approaches since all the available information is used simultaneously.

Assuming Dropouts are not Missing Completely at Random (MAR)

As noted above, especially for studies including a placebo arm, there is the potential for confounding between treatment arm and subject withdrawals due to uncontrolled asthma, that is, it is likely that dropouts are related to previous growth via the relationship of growth with lack of efficacy. The assumption that dropouts are MAR allows this relationship with past observations but assumes that dropout does not depend on future or the current unobserved values. Assuming dropouts are MAR, analyzing only the completers introduces dropout bias into the analysis. For growth studies where posttreatment failure measurements are not available, this dropout bias may not be completely removed, but its effect can be minimized. Some methods for performing the analysis and reducing the dropout bias are described here. The situation where postwithdrawal measurements are available is considered as well.

The mixed model approach, which uses individual height measures for each subject, allows the inclusion of height observations from the subjects who dropout before measurements cease to be taken. Regression parameter estimates are unbiased if dropouts are MAR because the dropout mechanism does not have to be explicitly modelled in a maximum likelihood approach. If dropout depends on the unobserved present or future observations, then the estimates will still be biased.

Under the assumption of MAR, the slope approach and the two-point approach yield slightly biased estimates because they require at least two observations. Unfortunately, there is a trade-off with including sub-

jects with minimal data. Estimating slopes from only a minimal number of observations close together in time introduces more variability. Since, unlike the mixed model approach, the data are reduced to one observation per subject, heterogeneity of variance becomes a concern.

The final scenario is that the missingness is neither MCAR nor MAR. In this case, none of the analyses presented here including the mixed model approach give unbiased estimates of the treatment differences. Assuming that estimated slopes possess a distribution centered at the true slopes, the slope and two-point approaches yield unbiased estimates. If the distributions of estimated slopes are only approximately centered at the true slopes, then the slope and two-point approaches using as much of the data as possible may yield less biased estimates than the other analyses presented here. This is because all subjects are given the same weight in the analysis regardless of how long they were in the study. Unfortunately, this reduced bias is at the cost of increased variability in the estimates. How to appropriately balance bias and variability is subjective and the problem is further illustrated in the example in the next section.

In studies where measurements continue to be recorded after treatment failure, these posttreatment failure observations can be included with the mixed model approach. This can be accomplished by use of an additional regressor and its interaction with time to describe heights occurring prior to or after treatment failure. If all subjects with treatment failure are administered the same medication, this regressor would have a value of '0' for heights prior to treatment failure and '1' for heights after treatment failure. More practically speaking, subjects experiencing treatment failure may have varying intensities of medication, depending on the intensity of the treatment failure. This could be accommodated in the analysis by replacing regressors of value '1' with a value matching the strength of the medication's effect on growth, for example, 1 = cromolyn, 2 = inhaled corticosteroid, 3 = prednisone burst.

Another way to address dropout bias is to include time in study as a regressor used with either the GLM or mixed model approach in an attempt to detect systematic differences in growth rate between completers and dropouts. However, due to the fact that it is believed that causes of dropout are correlated with the regressors, the introduction of this term into the model potentially causes a multicollinearity problem. This was in fact seen to be the case for the study examined below.

With missing values, a common approach is multiple imputation (34) where missing values are imputed multiple times to express the variability of the imputations. Complete data analyses are then performed and the results are aggregated in an appropriate fashion. Complications arise, however, when attempting to apply multiple imputation procedures to growth studies. Since it would be rare for two subjects to possess an identical set of regressors, fairly straightforward methods such as the approximate Bayesian bootstrap (35), cannot be applied directly. Also, if missing values are not missing at random as described by Rubin (35), the problem is further complicated. There is potential for a solution using multiple imputation, especially if the dropout mechanism can be modeled (36); however, more research is needed.

Illustration of Methods

The methods detailed above were applied to data from a double-blind study examining growth in prepubescent asthmatic children treated with fluticasone propionate (3). A total of 325 subjects, 244 males and 81 females, were enrolled in a year-long double-blind study and randomly assigned to a placebo, 50 µg BID, or 100 µg BID arm. Height was measured monthly throughout the study. A total of 57 subjects (including 55 completers) had Tanner scores >1, indicating the onset of puberty, and were dropped from the analysis, leaving a total of 268 subjects of which 208 had complete data. Of the 26 withdrawals attributed to lack of efficacy, 20 of those occurred in the placebo group.

Table 2 displays the results of the analyses. Variables included in the models were treatment, investigator, baseline growth rate, age, gender, age², and gender by age interaction. In addition, the mixed model included baseline growth rate by time, and treatment by time interactions. Nine analyses are displayed using these data, ordered from simplest (GLM on growth estimated by two-points approach) to most complex (mixed model) and then ordered by the number of subjects included in the analysis. Some general observations can be made.

As mentioned above, when comparing a corticosteroid treatment with placebo, the objective is to demonstrate equivalence or to estimate the difference between treatments. If one considers clinically meaningful bounds to be $\pm 1.0\text{cm/yr}$, then all analyses demonstrate equivalence. Nevertheless, it is still of interest to consider the amount of dropout bias in the analyses. Dropout bias is best indicated by comparing the estimated differences between placebo and active doses in the various analyses with the most unbiased (albeit least powerful) analyses. Without the assumption of MAR, these are the GLM two-points analysis (row 3) and the GLM slope approach (row 6). Under the assumption of MAR, the mixed model analysis on all the data would yield unbiased estimates (row 9). The MAR assumption, however, is probably not valid here since dropout is likely to depend on each subject's current level of asthma control. The condition of MCAR is even less likely to be true because subjects with uncontrolled asthma and thus slower growth are undoubtedly more likely to drop out. By comparing the results of the other analyses to the two in rows 3 and 6, and especially with the 100 μg versus placebo comparison, a fair amount of dropout bias is suggested. The analyses performed only on completers generally show the most dropout bias.

The effect of making the assumption of MCAR incorrectly is seen most noticeably by viewing the results from the weighted GLM (row 7). Here the estimated difference between the high dose and placebo is appre-

ciably higher than the estimates obtained from the other analysis methods.

To compare the power or discriminating ability of the various analyses, the widths of the 95% confidence intervals are compared. For this study, the mixed model approaches (rows 8 and 9) are the best from this perspective. For the other approaches, the ones that use as much of the data as possible (rows 3 and 6) or only completers (rows 1, 4, and 7) have more variability than the analyses that use subjects with at least 6 months of data (rows 2 and 5). This illustrates the trade off between bias and variability.

Since the assumptions that responses are normally distributed and that errors follow an AR(1) dependency structure are made in the mixed models approach (see Appendix), the parameter estimates were compared with those obtained from a GEE approach in Proc Genmod (33) with the same model except that subject is no longer treated as random yielding a slightly different correlation structure. Estimated treatment differences from this approach were quite similar to the estimates from the mixed model approach, indicating that the assumptions made in the mixed model approach in addition to those made in the GEE approach do not cause the results to differ appreciably.

DISCUSSION

While measuring a child's height at one time point is a relatively simple procedure, assessing the impact of corticosteroid treatment on growth in asthmatic children is complex since both drug and disease, among other factors, may affect growth rate. We offer here our general recommendations for growth study design and analysis, as well as specifics for investigating the growth effects of a drug in a disease known to impact the same system. While there have been effects seen at higher doses or with older agents that are likely to be beyond the level of impact from disease, it may be overly diligent to cause concern over differences that may be primarily a matter of a design flaw. For this reason,

TABLE 2
Comparison of Analysis Procedures

Analysis Method	Method to Estimate Growth	Analysis Population (N)	Contrasts					
			50 µg Dose—Placebo			100 µg Dose—Placebo		
			Estimate	95% CI	Width of CI	Estimate	95% CI	Width of CI
1. <i>GLM</i>	<i>Two-points</i>	<i>Completers (208)</i>	-0.24	(-0.67, 0.19)	0.86	-0.46	(-0.88, -0.03)	0.85
2. GLM	Two-points	≥7 obs (232)	-0.22	(-0.62, 0.19)	0.81	-0.37	(-0.76, 0.02)	0.78
3. GLM	Two-points	≥2 obs (261)	-0.20	(-0.66, 0.26)	0.92	-0.27	(-0.71, 0.16)	0.87
4. <i>GLM</i>	<i>Slope</i>	<i>Completers (208)</i>	-0.16	(-0.59, 0.28)	0.86	-0.43	(-0.85, -0.00)	0.85
5. GLM	Slope	≥7 obs (232)	-0.18	(-0.58, 0.21)	0.79	-0.40	(-0.78, -0.02)	0.76
6. GLM	Slope	≥2 obs (261)	-0.14	(-0.59, 0.31)	0.90	-0.28	(-0.71, 0.16)	0.86
7. <i>Weighted GLM</i>	<i>Slope</i>	<i>Completers (208)</i>	-0.22	(-0.63, 0.18)	0.81	-0.57	(-0.97, -0.18)	0.79
8. <i>Mixed model</i>		<i>Completers (208)</i>	-0.22	(-0.53, 0.08)	0.61	-0.41	(-0.71, -0.10)	0.61
9. Mixed model		≥1 obs (268)	-0.22	(-0.50, 0.06)	0.56	-0.39	(-0.67, -0.11)	0.55

The mixed models analysis on all of the data used 3267 observations from 268 subjects. The mixed models analysis on completers used 2912 observations from 208 subjects.

CI = confidence interval. All values are in cm/yr. Note that analyses in italics are on completer subjects only. These analyses are most affected by the confounding of treatment group with dropout rate and are included here for comparison.

future growth studies must attempt to minimize this problem.

Criticisms have been made with respect to this design flaw in interpretation of results (15). We believe, however, that the upcoming FDA recommendation to move away from assessing whether a drug does or does not have an effect (a *p*-value) towards an investigation of where a drug lies on a continuum (a confidence interval) (16) is a sound approach.

The upcoming guidance is expected to recommend that mild persistent asthmatics be the focus of growth studies, and that subjects continue to be measured for height regardless of treatment failure. This seems a reasonable goal from the viewpoint of minimizing dropouts in a cromolyn or nedocromil control group in light of asthma control guidelines (8), but it is still possible that nonrandom dropouts will occur. Whether it is feasible to develop inclusion/exclusion criteria in order to target this mild persistent group is currently an open question. If mild intermittent subjects are enrolled, these patients are not indicated for inhaled corticosteroids and have greater potential for growth effects due to more peripheral (alveolar) penetration of drug within the lungs, hence potentially greater systemic absorption compared to patients with more severe asthma (28). Conversely, if moderate persistent subjects are enrolled, the nonrandom dropout problem becomes more of an issue.

A possible alternative is to allow subjects to receive standard asthma therapy, including prednisone bursts, after treatment failure. This approach would allow prescribing physicians and parents to assess the tradeoffs of both efficacy and growth between asthma control via inhaled corticosteroids, and lack of asthma control and associated prednisone bursts. An analysis method that can accommodate this design enhancement is the mixed model approach adapted to account for post treatment failure observations.

Under the assumptions of MCAR or MAR missingness, the mixed model approach provides unbiased estimates of the difference between treatment effects on growth that are

the least variable of the approaches considered. When missingness is neither MCAR nor MAR, the GLM slope approach performed on as much of the data as possible provides the least biased estimates but at the cost of high variability. In this circumstance, it is less clear what the best solution should be. There is a trade-off between either decreasing the variance by using only subjects with a minimum amount of data (eg, 4–6 months) or decreasing the variance by using a mixed model approach and decreasing the amount of bias in the estimates.

As in most clinical studies, it is essential to have a well-designed trial in order to eliminate as many of the potential analysis problems as possible. This includes careful measurement of height and assessment of key demographic, environmental, and disease factors that may influence a child's growth. In addition, designing studies to minimize dropouts (by comparing only treatment arms that offer reasonable asthma control) and continuing to measure subjects who dropout minimizes the bias caused by early withdrawals.

In summary, care must be taken in the design and analysis of growth studies to provide results that are free from confounding effects due to nonrandom dropouts and imbalances in treatment allocation with respect to demographic and environmental parameters, such as puberty and socio-economic status. This will provide physicians and parents with a clearer understanding of the benefits and risks associated with various asthma medication alternatives.

The potential for disease effects to be confounded with drug treatment effects also needs to be considered (37). Perhaps inclusion of some measure of asthma control in the analysis is a potential solution. Further research is needed on this aspect of the design and analysis of growth studies.

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APPENDIX

Here details of the mixed model approach are given. The mixed model for the i^{th} subject is

$$Y_i = X_i\beta + Z_iU + E_i$$

where Y_i is the $m_i \times 1$ vector of heights, containing $m_i \leq m$ observations taken at some or all of m fixed points in time. X_i is the $m_i \times p$ design matrix and β is a $p \times 1$ vector of parameters including age, age², gender, age*gender, investigator, treatment, time, treatment*time, baseline rate, and baseline rate*time. Z_i is the $m_i \times q$ random effects design matrix (Z_i is a $m_i \times 1$ vector of ones when subject is the only random effect). U_i is a $q \times 1$ vector containing the random effects. When $q = 1$, U_i is a random intercept term.

The mixed model assumes that U_i and E_i are independent and multivariate normal with respective variances G and R_i . These assumptions imply that $\text{Var}(Y_i) = Z_iGZ_i^T + R_i$. Thus, the intra-subject correlation is accounted for with nondiagonal R_i , or through U_i . Under exchangeability (compound symmetry), the error variance-covariance matrix R_i for each subject would look like

$$\begin{bmatrix} \sigma_e^2 & \rho\sigma_e^2 & \dots & \rho\sigma_e^2 \\ \rho\sigma_e^2 & \sigma_e^2 & \ddots & \vdots \\ \vdots & \ddots & \ddots & \rho\sigma_e^2 \\ \rho\sigma_e^2 & \dots & \rho\sigma_e^2 & \sigma_e^2 \end{bmatrix}$$

With an AR(1) structure, the error variance covariance matrix for each subject would look like

$$\begin{bmatrix} \sigma_e^2 & \rho\sigma_e^2 & \rho^2\sigma_e^2 & \dots & \rho^{m-1}\sigma_e^2 \\ \rho\sigma_e^2 & \sigma_e^2 & \ddots & \ddots & \vdots \\ \rho^2\sigma_e^2 & \ddots & \ddots & \ddots & \rho^2\sigma_e^2 \\ \vdots & \ddots & \ddots & \sigma_e^2 & \rho\sigma_e^2 \\ \rho^{m-1}\sigma_e^2 & \dots & \rho^2\sigma_e^2 & \rho\sigma_e^2 & \sigma_e^2 \end{bmatrix}$$

When in addition to specifying a structure for the errors, subject is treated as random, the variance covariance matrix for each subject has an additional parameter σ_u^2 added to every term in the matrix. This yields a correlation structure where each pair of observations from the same subject are considered correlated to at least some degree, with observations closer together in time being more correlated.

When heights are used as the response, the within-subject effect of time becomes of interest. More specifically, the treatment*time interaction answers the question of differing rates and is used as a basis for estimates and confidence intervals on the treatment differences.

SAS Code

```
PROC MIXED DATA = dataset;
  CLASS trtgp invest gender patient;
  MODEL height = trtgp invest gender age agesqrd
    baserate time age*gender
    baserate*time time*trtgp/s;
  REPEATED/type = ar(1) subject=patient rcorr;
  RANDOM patient; *adds the exchangeable component to the correlation structure;
  PARMS 25 .5 .5; *initial estimates of between subject var, AR(1) parm, and residual var respectively;
  ESTIMATE 'Placebo vs 50' trtgp*time - 1 1 0/cl;
  ESTIMATE 'Placebo vs 100' trtgp*time - 1 0 1/cl;
RUN;
```

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