

A COMPARISON OF BECLOMETHASONE, SALMETEROL, AND PLACEBO IN CHILDREN WITH ASTHMA

F. ESTELLE R. SIMONS, M.D.,

AND THE CANADIAN BECLOMETHASONE DIPROPIONATE-SALMETEROL XINAFOATE STUDY GROUP*

ABSTRACT

Background An inhaled glucocorticoid is currently the medication of choice for long-term control of persistent asthma in children. The role of long-acting β_2 -adrenergic-receptor agonists, such as salmeterol, needs to be defined.

Methods We conducted a randomized, double-blind, placebo-controlled, parallel-group, one-year study of 241 children (mean [\pm SD] age, 9.3 ± 2.4 years) with clinically stable asthma and less than one month of prior glucocorticoid use. We compared inhaled beclomethasone dipropionate (200 μ g twice daily) with salmeterol xinafoate (50 μ g twice daily) and placebo (lactose). The primary outcome measure, airway responsiveness (as assessed with a methacholine challenge), was evaluated before treatment; after 3, 6, 9, and 12 months of treatment (12 and 36 hours after study medications had been withheld); and 2 weeks after the end of treatment. Spirometry, symptoms, use of rescue medication (200 μ g of albuterol inhaled as needed), and adverse effects were also assessed.

Results During months 1 through 12 overall, beclomethasone was associated with significantly less airway hyperresponsiveness than salmeterol ($P=0.003$) or placebo ($P<0.001$). This effect was lost two weeks after treatment had been stopped. As compared with placebo, beclomethasone was associated with less variability between morning and evening in the peak expiratory flow ($P=0.002$), as was salmeterol ($P=0.02$). Beclomethasone was also associated with a reduced need for albuterol as rescue therapy ($P<0.001$) and fewer withdrawals because of asthma exacerbations ($P=0.03$), but salmeterol was not ($P=0.09$ and $P=0.55$, respectively). During months 1 through 12, linear growth was 3.96 cm in the children receiving beclomethasone, as compared with 5.40 cm in the salmeterol group ($P=0.004$) and 5.04 cm in the placebo group ($P=0.018$). Height was not measured after treatment ended.

Conclusions Beclomethasone was effective in reducing airway hyperresponsiveness and in controlling symptoms of asthma, but it was associated with decreased linear growth. Salmeterol was not as effective as beclomethasone in reducing airway hyperresponsiveness or in controlling symptoms; however, it was an effective bronchodilator and was not associated with rebound airway hyperresponsiveness, masking of symptoms, or adverse effects. (N Engl J Med 1997;337:1659-65.)

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AN inhaled glucocorticoid is currently the medication of choice for long-term control of persistent asthma in children.^{1,2} There are surprisingly few comprehensive assessments of the benefits and risks of these medications in children over a period of one year or longer.³⁻⁶ Beclomethasone dipropionate has been used for the treatment of asthma in children for more than two decades and is considered to be safe for long-term use.⁷

In contrast, the role of long-acting β_2 -adrenergic-receptor agonists such as salmeterol xinafoate is not yet established in children, and according to some guidelines, these medications should be used only in children receiving treatment with inhaled glucocorticoids.^{1,2} Although single-dose and short-term studies in children have shown that long-acting β_2 -adrenergic agonists provide excellent bronchodilation and decrease airway hyperresponsiveness,⁸⁻¹³ some loss of the bronchoprotective effect has been reported.^{11,12}

In a one-year, placebo-controlled study, we tested the hypothesis that treatment with beclomethasone or salmeterol is beneficial in controlling asthma in children.

METHODS

We performed a randomized, double-blind, parallel-group, multicenter comparison of beclomethasone (Beclodisk, Glaxo Wellcome, Mississauga, Ont., Canada; 200 μ g), salmeterol xinafoate (Serevent, Glaxo Wellcome; 50 μ g), and placebo (lactose) administered twice daily for one year in children with persistent asthma. The protocol was approved by the institutional review boards at all the study sites. The study was conducted from August 1992 to November 1995.

Before enrollment, oral consent was obtained from the children, written informed consent was obtained from their parents, and their primary care physicians were contacted. Data collection was standardized and monitored throughout the study by Glaxo Wellcome to ensure completeness and prevent bias caused by local variations in procedures.

A total of 315 children with asthma (age range, 6 to 14 years) were enrolled. Inclusion criteria were clinically stable asthma, less than one month of treatment at any time with inhaled or oral glucocorticoids for asthma, no glucocorticoid treatment for asthma within three months before enrollment, a forced expiratory volume in one second (FEV₁) of more than 70 percent after the broncho-

From the Children's Hospital of Winnipeg, 820 Sherbrook St., Winnipeg, MB R3A 1R9, Canada, where reprint requests should be addressed to Dr. Simons.

*The members of the Canadian Beclomethasone Dipropionate-Salmeterol Xinafoate Study Group are listed in the Appendix.

dilator had been withheld for 6 hours, a 10 percent increase in FEV₁ 30 minutes after the inhalation of 400 µg of albuterol, the requirement of less than 8 mg of methacholine per milliliter to decrease the FEV₁ by 20 percent (PC₂₀), and the ability to refrain from using study medications for 36 hours and from using rescue albuterol for 6 hours before visits. Exclusion criteria were any emergency department visits or hospitalizations for asthma within the prior three months, a history of life-threatening asthma, and a history of adverse reactions to the medications used in the study.

Study Design

Each child completing the 56-week study was assessed at least 15 times. All assessments took place in the morning. The 52-week, double-blind treatment period was preceded and followed by a 2-week period during which data were collected but no study medication was given. Throughout the study, the use of inhaled albuterol (Ventodisk, Glaxo Wellcome; 200 µg), as needed, was recorded. If the child was using cromolyn sodium, nedocromil, or theophylline for asthma or topical glucocorticoids or histamine H₁-receptor antagonists for allergic rhinitis or atopic dermatitis, these medications were permitted in unchanged doses.

At the end of the run-in period, children were randomly assigned to twice-daily treatment with beclomethasone, salmeterol, or placebo, administered as a dry powder through a Diskhaler device, followed by rinsing, gargling with water, and expectorating.

Assessment of Airway Responsiveness

The primary outcome measure, airway responsiveness, was assessed at base line (visit 2), before the study medications were given; after 3, 6, 9, and 12 months of treatment (visits 5, 8, 11, and 14, respectively); and 2 weeks after the study medications had been discontinued (visit 15). At all these visits, airway responsiveness was assessed six or more hours after the use, if any, of albuterol as rescue therapy. During treatment, airway responsiveness was assessed 12 hours after study medications had been withheld and also at 36 hours, when the bronchodilator effect of salmeterol was absent.

Methacholine-challenge tests were performed in an identical manner at each study site, with the use of an adaptation⁸ of the method of Cockcroft et al.¹⁴ Children inhaled aerosolized methacholine, diluted in 0.9 percent saline, by breathing at tidal volume from a face mask for two minutes. The FEV₁ was assessed 30 seconds, 90 seconds, and 3 minutes after the completion of the methacholine inhalation. The lowest FEV₁ value from a technically acceptable flow-volume loop was considered to be the response to methacholine. The FEV₁ after inhalation of 0.9 percent saline served as the base-line value for the dose response to methacholine. At intervals of no less than five minutes, the methacholine dose was doubled. The PC₂₀ was calculated by interpolation from a log linear graph. Testing was deferred if the child had symptoms of asthma or an FEV₁ that was less than 70 percent of the predicted value during the visit or if treatment with prednisone had been required during the preceding two weeks.

Spirometric Studies

Spirometry was performed before each assessment of airway responsiveness, with the use of a dry rolling-seal spirometer that met American Thoracic Society standards.¹⁵ FEV₁, forced vital capacity, and midexpiratory flow at 25, 50, 75, and 25 to 75 percent of the forced vital capacity (FEF_{25%}, FEF_{50%}, FEF_{75%}, and FEF_{25-75%}) were determined.¹⁶

Assessment of Asthma Symptoms and Peak Expiratory Flow

The children recorded twice daily on diary cards their use of albuterol (200 µg) for breakthrough wheezing, symptoms of asthma, absences from school, and night waking. Every morning and evening, before any medication was taken, peak expiratory

flows were measured in triplicate at home with the use of a Mini-Wright peak-flow meter (Armstrong Medical Industries of Canada, Scarborough, Ont.). The highest value was recorded.

Diary cards were reviewed during visits 3, 4, 6, 7, 9, 10, 12, and 13. Between visits, the study nurse telephoned the children's parents regularly. Compliance was monitored by counting the number of medication blisters used.

Management of Asthma Exacerbations

The children's parents were provided with a 24-hour emergency telephone number. Children who had exacerbations of asthma between visits 1 and 2 were withdrawn from the study before being randomly assigned to a treatment group. After visit 2, children who had exacerbations of asthma, defined as the presence of symptoms despite study medication and the use of albuterol as rescue therapy, could remain in the study if they had a response to treatment with prednisone (1 mg per kilogram of body weight; maximal dose, 60 mg per day) for five to seven days. The children were withdrawn from the study if the symptoms were not controlled with prednisone, if more than one course of prednisone per month or more than four courses during the year were required, or if hospitalization for asthma was required. Data obtained during treatment with prednisone were not included in the statistical analysis.

Laboratory Tests

During visits 2, 8, and 14, a complete blood count, eosinophil count, measurement of serum eosinophilic cationic protein (Kabi Pharmacia Diagnostics, Uppsala, Sweden), blood-chemistry tests, and urinalysis were performed.

Adverse Effects

Adverse effects were reviewed during all visits. Heart rate and blood pressure were recorded, and tremor was assessed. During visits 1, 5, 8, 11, and 14, height was measured by the same trained observer at each site. A calibrated stadiometer was used at most study sites. Height was not measured after the study medications had been discontinued.

Statistical Analysis

No interim analyses were performed. All statistical tests were two-sided and were carried out at the 5 percent level of significance.^{17,18} Data on demographic characteristics and base-line airway responsiveness and pulmonary function were summarized descriptively for each treatment group.

The PC₂₀ values for methacholine at 12 and 36 hours were analyzed with the use of repeated-measures analysis of variance to compare the responses at months 3, 6, 9, and 12. Analyses were conducted with the use of a log scale, and the model included the effects of the study site and treatment. Age and height at base line and, for PC₂₀ at 12 hours, the base-line PC₂₀ value were covariates.

FEV₁, forced vital capacity, FEF_{25%}, FEF_{50%}, FEF_{75%}, FEF_{25-75%}, and peak expiratory flow were analyzed with the use of repeated-measures analysis of variance to compare the values at months 3, 6, 9, and 12 with the base-line values. Analyses were performed with the use of raw data, and the model included the effects of the study site and the assigned treatment. Age and height at base line and the base-line pulmonary-function values were covariates.

A value for the peak expiratory flow in the morning (measured at home) was calculated at each visit as the mean highest value during the interval since the preceding visit, and the mean values for each visit were compared. Similar analyses were performed for the peak expiratory flow in the evening and for the variation between the morning and evening values, calculated for each patient on each day as follows:

$$\frac{(\text{evening value} - \text{morning value})}{\text{evening value}}$$

Using the Wilcoxon rank-sum test, we compared the treatment groups with respect to the percentage of days free from the use of albuterol as rescue therapy, the amount of albuterol used, the percentage of days on which asthma affected activity, the percentage of school days missed, and the percentage of nights when the child awakened with asthma. Withdrawals from the study were analyzed with the use of the log-rank test.

Growth rate was calculated for each child as the regression coefficient of height on time, expressed in centimeters per month, and analyzed by analysis of covariance. The model included the effects of sex, study site, and assigned treatment. Age and height at base line were covariates.

RESULTS

Of the 315 children enrolled in the study, 74 (23 percent) were not randomly assigned to treatment groups because they did not meet all the enrollment criteria (58 children), had an exacerbation of asthma (7), or dropped out (9). Thus, 241 children were randomly assigned to treatment groups. The three groups were similar with regard to demographic characteristics, base-line airway responsiveness, and spirometric values (Table 1).

Airway Responsiveness

Geometric mean PC₂₀ values for methacholine obtained 12 hours after inhalation of the study drug are shown in Figure 1. During months 1 through 12 overall and at 3, 6, 9, and 12 months, beclomethasone treatment was associated with more than a doubling of the PC₂₀ value, a significantly greater

improvement in airway responsiveness than that associated with placebo (P<0.001). As compared with salmeterol, beclomethasone treatment reduced airway hyperresponsiveness significantly during months 1 through 12 overall (P=0.003) and at 6, 9, and 12 months. Two weeks after treatment ended, the effectiveness of beclomethasone had waned. During months 1 through 12 overall, salmeterol and placebo reduced airway hyperresponsiveness to a similar degree (P=0.58) but resulted in less than a doubling of the PC₂₀ value. The effect of salmeterol on airway responsiveness did not change significantly during treatment. Stopping salmeterol was not associated with a significant increase in airway responsiveness.

The mean PC₂₀ values obtained 36 hours after inhalation of the study medication are also shown in Figure 1. During months 1 through 12 overall, the improvement in airway responsiveness produced by beclomethasone was greater than that produced by salmeterol (P=0.02), but neither the effect of beclomethasone nor the effect of salmeterol differed significantly from that of placebo (P=0.20 and P=0.26, respectively). At 6 and 12 months, beclomethasone improved airway responsiveness to a significantly greater degree than did salmeterol or placebo.

Spirometric Studies

During months 1 through 12 overall and at 3, 6, 9, and 12 months, both beclomethasone and salme-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE TREATMENT GROUPS.*

CHARACTERISTIC	BECLOMETHASONE (N=81)	SALMETEROL (N=80)	PLACEBO (N=80)	TOTAL (N=241)
Male sex (% of children)	59	60	55	58
Age (yr)	9.6±2.6	8.8±2.1	9.5±2.4	9.3±2.4
Height (cm)	140.0±14.7	134.6±12.1	138.5±14.5	137.7±13.9
Weight (kg)	37.6±13.7	33.6±11.5	35.9±12.7	35.7±12.7
Allergic rhinitis (% of children)	69	71	70	70
Atopic dermatitis (% of children)	38	45	35	39
History of medications for rhinitis or dermatitis (% of children)	58	56	56	57
Other asthma medications (% of children)†	22	26	26	25
PC ₂₀ for methacholine (mg/ml)‡	0.83	0.76	0.83	
FEV ₁ (liters)	1.89±0.61	1.76±0.46	1.88±0.58	
FEV ₁ (% of predicted value)	92±13	95±13	96±16	
Forced vital capacity (liters)	2.32±0.77	2.12±0.58	2.26±0.69	
FEF _{25%} (liters/sec)	3.15±1.13	3.21±0.98	3.17±1.13	
FEF _{50%} (liters/sec)	1.95±0.83	2.01±0.67	2.00±0.76	
FEF _{75%} (liters/sec)	0.91±0.44	0.90±0.34	0.95±0.41	
FEF _{25-75%} (liters/sec)	1.89±0.73	1.86±0.61	1.90±0.68	
Peak expiratory flow (liters/min)	268±86	246±63	258±77	

*Plus-minus values are means ±SD.

†Medications included cromolyn sodium (in 19 percent of the children), nedocromil (in 1 percent), theophylline (in 1 percent), and β₂-agonists used regularly (in 3 percent).

‡Values shown are geometric means.

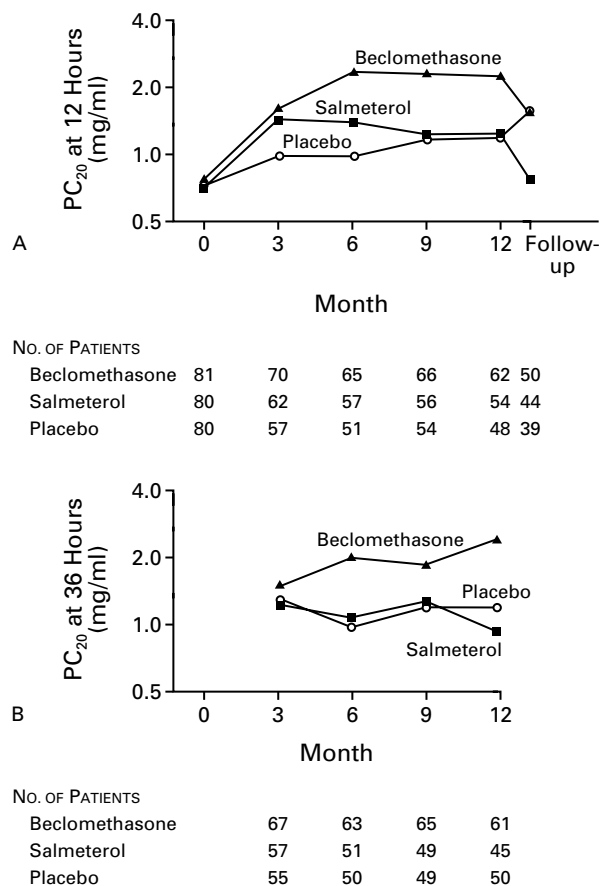


Figure 1. Geometric Mean PC₂₀ Values for Methacholine, Measured 12 Hours (Panel A) and 36 Hours (Panel B) after Inhalation of the Study Medication in Children with Asthma Randomly Assigned to Treatment with Beclomethasone, Salmeterol, or Placebo.

The primary outcome measure, protection against methacholine-induced bronchoconstriction, was assessed at base line and follow-up (2 weeks after the end of treatment) and at 3, 6, 9, and 12 months. When the PC₂₀ for methacholine was measured 12 hours after inhalation of the study medication, the protection afforded by beclomethasone, expressed as the change from the base-line value, was significantly greater than that afforded by placebo at 3 months (P=0.01), 6 months (P<0.001), 9 months (P=0.01), and 12 months (P=0.004) and significantly greater than that afforded by salmeterol at 6 months (P=0.02), 9 months (P=0.02), and 12 months (P=0.01). When the PC₂₀ was measured 36 hours after inhalation of the study medication, the protection afforded by beclomethasone was significantly greater than that afforded by salmeterol and placebo at 6 months (P=0.02 and P=0.01, respectively) and 12 months (P=0.001 and P=0.009, respectively). The effect of salmeterol and placebo on airway hyperresponsiveness, measured at 12 and 36 hours, did not differ significantly at any time during the study.

terol produced significant increases in FEV₁, FEF_{25%}, FEF_{50%}, FEF_{75%}, and peak expiratory flow but not in forced vital capacity, as compared with placebo (Table 2). The effects of beclomethasone and salmeterol were similar for all measurements.

Peak Expiratory Flow Monitored at Home

During months 1 through 12 overall, both beclomethasone and salmeterol increased the morning peak expiratory flow significantly as compared with placebo (P=0.02 and P<0.001, respectively) (Table 2), and the effects of the two drugs were similar (P=0.16). Salmeterol increased the mean evening peak expiratory flow significantly as compared with placebo (P=0.01), but beclomethasone did not (P=0.41). The peak expiratory flow varied significantly less in the beclomethasone group and in the salmeterol group than in the placebo group (P=0.002 and P=0.02, respectively); the effects of beclomethasone and salmeterol were similar (P=0.50).

Control of Asthma Symptoms

During months 1 through 12 overall, the control of asthma symptoms was better in the children receiving beclomethasone than in those receiving salmeterol or placebo (Tables 3 and 4). As compared with the placebo group, the beclomethasone group had a significantly higher percentage of days and nights free from the use of albuterol, a significantly higher percentage of children requiring no albuterol, and a significantly lower rate of withdrawal because of asthma exacerbations. The numbers of courses of prednisone in the beclomethasone, salmeterol, and placebo groups were 10, 15, and 17, respectively. Compliance with the medication regimen was excellent in all three groups.

Laboratory Tests

After 12 months, the mean eosinophil count was 5.6 percent in the children receiving beclomethasone, 7.9 percent in those receiving salmeterol, and 7.0 percent in those receiving placebo. During months 1 through 12 overall, the children receiving beclomethasone had lower eosinophil counts than those receiving placebo (P=0.01) or salmeterol (P<0.001). There were no significant differences in serum eosinophilic cationic protein levels or other blood-chemistry values among the treatment groups.

Adverse Effects

There were no clinically significant differences in adverse effects among the treatment groups. Tremor and changes in heart rate and blood pressure were infrequently noted. The most commonly reported problems were upper respiratory tract infections, throat irritation, and headaches.

During months 1 through 12 overall, height in-

TABLE 2. ADJUSTED OVERALL MEAN CHANGES IN SPIROMETRIC VALUES AND PEAK EXPIRATORY FLOW DURING MONTHS 1 THROUGH 12.*

VARIABLE	BECLOMETHASONE	SALMETEROL	PLACEBO
FEV ₁ (% of predicted value)	10†	10‡	5
FEV ₁ (liters)	0.19‡	0.20‡	0.08
Forced vital capacity (liters)	0.14	0.16	0.12
FEF _{25%} (liters/sec)	0.54§	0.70‡	0.25
FEF _{50%} (liters/sec)	0.41‡	0.45‡	0.14
FEF _{75%} (liters/sec)	0.27‡	0.22‡	0.06
FEF _{25-75%} (liters/sec)	0.43‡	0.40‡	0.16
Peak expiratory flow (liters/min)			
At clinic	18¶	26‡	-1
At home, morning	35	41‡	25
At home, evening	28	35**	25
Variation between morning and evening	-0.02¶	-0.01	-0.01

*Values are based on repeated-measures analysis of variance.

†P=0.001 for the comparison with placebo.

‡P<0.001 for the comparison with placebo.

§P=0.003 for the comparison with placebo.

¶P=0.002 for the comparison with placebo.

||P=0.02 for the comparison with placebo.

**P=0.01 for the comparison with placebo.

TABLE 3. OVERALL CONTROL OF ASTHMA SYMPTOMS AND COMPLIANCE WITH TREATMENT DURING MONTHS 1 THROUGH 12.

VARIABLE	BECLOMETHASONE	SALMETEROL	PLACEBO
Albuterol not required (% of days and nights)	92*	88	83
Albuterol not required (% of children)	95†	91	84
No school missed because of asthma (% of children)	81	88	66
Activities affected by asthma (% of days)‡	1	2	2
Waking (% of nights)‡	1	1	1
Compliance >75% (% of children)	100	99	99

*P<0.001 for the comparison with placebo by the Wilcoxon rank-sum test.

†P=0.03 for the comparison with placebo by the Wilcoxon rank-sum test.

‡The median values are low because all the children had mild or moderate asthma.

TABLE 4. DURATION OF PARTICIPATION IN THE STUDY AND REASONS FOR WITHDRAWAL AFTER RANDOMIZATION.

VARIABLE	BECLOMETHASONE	SALMETEROL	PLACEBO	OVERALL AVERAGE
Diary card completed (no. of patient-days, including run-in period)	26,739	24,456	23,124	—
Study medication taken (no. of days)*	304±81	279±103	263±114	—
Withdrawal after randomization (% of children)	17†	28	31	25
Primary reason for withdrawal (% of children)				
Asthma exacerbation	5	15	15	12
Adverse event	4	5	4	4
Noncompliance or protocol violation	2	2	4	3
Other	6	6	8	6

*Values are means ±SD.

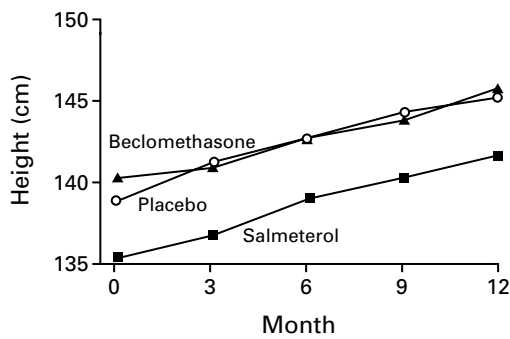
†P=0.03 for the comparison with the placebo group.

creased by 3.96 cm in the beclomethasone-treated children, which was significantly less than the height increases in the placebo-treated children (5.04 cm, P=0.018) and the salmeterol-treated children (5.40 cm, P=0.004) (Fig. 2). There was no significant effect of the study site on height (P=0.22).

DISCUSSION

We compared the effects of beclomethasone, salmeterol, and placebo administered through a dry-powder inhaler for one year in children with mild or moderate persistent asthma. During the study, there was a trend toward improvement in most of the outcome measures, including PC₂₀ and spirometric values, in all the children, even those receiving placebo.

Our study differs in several aspects from previous controlled comparisons of an inhaled glucocorticoid with a β_2 -agonist or theophylline for at least one year in children with asthma. None of the children in our study used glucocorticoids regularly for asthma before enrollment. In addition, our study included a placebo group in which a short-acting β_2 -agonist was used as needed. Study medications were administered twice daily, with careful attention to rinsing, gargling, and expectorating after each use. We measured airway responsiveness 12 and 36 hours after the medication had been administered. In other studies, previous regular use of glucocorticoids was not an exclusion criterion,³ the children were not randomly assigned to double-blind treatment,⁴ or there was no placebo group.³⁻⁶ In these studies, the inhaled glucocorticoid was given three or four times daily,^{3,5} an inhaled short-acting β_2 -adrenergic agonist was given regularly two or three times daily,^{3,4} or the interval between the administration of



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Beclomethasone	81	76	73	70	67
Salmeterol	80	70	65	63	58
Placebo	80	68	60	57	55

Figure 2. Mean Height at Base Line and after 3, 6, 9, and 12 Months of Treatment.

Overall, during months 1 through 12, the mean increase in height was 3.96 cm in the beclomethasone group, 5.40 cm in the salmeterol group, and 5.04 cm in the placebo group. The effect of beclomethasone on height appeared to be greatest during months 1 through 3. After this period, the slopes of the lines were parallel for the three treatment groups. The effect of beclomethasone on growth differed significantly from the effect of placebo at 6 months ($P=0.002$), 9 months ($P<0.001$), and 12 months ($P<0.001$) and differed significantly from the effect of salmeterol at 9 and 12 months ($P<0.001$ for both comparisons). The effect of salmeterol on growth did not differ significantly from that of placebo at any time.

the study medication and the assessment of airway hyperresponsiveness was not specified.^{3,5} Despite a variety of study designs and comparisons, inhaled glucocorticoids were more effective for symptom control in all the studies, with less use of rescue medication and improved airway patency,³⁻⁶ and airway hyperresponsiveness was decreased in two of the studies,^{3,6} but not in one.⁵

In the beclomethasone-treated children in our study, airway hyperresponsiveness continued to improve throughout the treatment period, but the improvement disappeared two weeks after the medication had been discontinued, confirming previous reports that inhaled glucocorticoids ameliorate but do not cure childhood asthma.^{19,20}

Our study provides new information about salmeterol treatment in children. In previous studies,¹¹⁻¹³ a regimen of 25 to 50 μg of salmeterol twice daily for one to four months was associated with an excellent bronchodilator effect, decreased airway hyperresponsiveness, and a reduced need for bronchodilator treatment. In two studies,^{11,12} the improvement in exercise- or methacholine-induced airway hyperresponsiveness found after the initial dose was not maintained throughout the period of salmeterol treatment; the clinical importance of this finding is unknown. In our one-year study, salmeterol was less

effective than beclomethasone in improving airway hyperresponsiveness and preventing symptoms, but it was an effective bronchodilator and did not appear to mask symptoms or increase airway hyperresponsiveness after the cessation of treatment.

In our study, beclomethasone had systemic activity, as manifested by decreased blood eosinophil counts and linear growth, despite the moderate dose of 11.8 μg per kilogram per day and the precautions taken to reduce absorption from the oropharynx and gastrointestinal tract. This finding contrasts with the outcome of a meta-analysis⁷ of 21 studies conducted before 1992, and with the results of older long-term, prospective, nonrandomized studies,^{21,22} in which children with more severe persistent asthma may have been enrolled and in which no adverse effect on linear growth was observed. In other studies, delayed linear growth either was not observed^{4,23} or was noted but attributed to asthma-associated delayed puberty rather than to the effect of inhaled glucocorticoids.²⁴ A retrospective, population-based study reported normal adult height despite the use of glucocorticoids in childhood.²⁵ Our finding of an effect on linear growth confirms the findings in some brief reports,²⁶⁻²⁸ retrospective studies,²⁹ and prospective studies,^{5,30-33} including two randomized, double-blind studies^{5,33} in which inhaled glucocorticoids were administered for at least six months. In these studies,^{5,26-33} the glucocorticoid, generally beclomethasone, was administered in doses of 400 to 1500 μg per day, with the use of a metered-dose inhaler with or without a spacer device or with the use of a dry-powder inhaler. Oropharyngeal rinsing after the administration of inhaled glucocorticoids may not have been emphasized. In some of these studies, as in ours, the effect on linear growth was apparent within months after the initiation of treatment with inhaled glucocorticoids.^{29,31,33} In most studies, including ours, height was not monitored after the discontinuation of glucocorticoid treatment. In a study in which children received beclomethasone for only seven months and height was measured four months after the drug had been discontinued, no catch-up growth was reported.³³

Our study provides confirmation that inhaled glucocorticoids are effective for the long-term control of persistent childhood asthma.^{3-6,34} In children with moderate or severe persistent asthma, these medications are without equal for reducing symptoms and the need for hospitalization. For children with mild persistent asthma, however, a difficult choice must be made between medications that provide excellent symptom control with the possibility of a minimal influence on linear growth and those that are less effective in controlling symptoms but have no effect on linear growth. The lowest maintenance dose of an inhaled glucocorticoid that eliminates the symptoms of asthma should therefore be prescribed, and

height should be monitored regularly. In view of the current trends toward starting treatment with inhaled glucocorticoids early in the course of childhood asthma^{4,35} and using daily doses higher than 400 µg of beclomethasone or the equivalent for long periods of time, randomized, controlled, double-blind studies of inhaled glucocorticoids used for many years are needed.

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APPENDIX

The following physicians participated in the Canadian Beclomethasone Dipropionate-Salmeterol Xinafoate Study: J. Dolovich (Hamilton, Ont.; deceased), D.W. Moote (London, Ont.), J.A. Mazza (London, Ont.), B. Lyttle (London, Ont.), A.B. Becker (Winnipeg, Man.), W.T.A. Watson (Winnipeg, Man.), M. Gold (Toronto), R. Zinman (Halifax, N.S.), S.J. Feanny (Toronto), A. Ferguson (Vancouver, B.C.), D.W. Cockcroft (Saskatoon, Sask.), B. Taylor (Saskatoon, Sask.), J. Bouchard (La Malbaie, Que.), F. Simard (Chicoutimi, Que.), S. Lavi (Toronto), and B. Mazer (Montreal).

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