



ORIGINAL ARTICLE

Growth and Pituitary-Adrenal Function in Children with Severe Asthma Treated with Inhaled Budesonide

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Corticosteroids are potent antiinflammatory agents, and administering them by aerosol has been recommended as the treatment of choice for patients with severe persistent asthma¹. The use of inhaled corticosteroids in young children has been limited, however, by the technical difficulty of administration and the paucity of data about the safety of these drugs. The introduction of various spacer devices has allowed inhaled corticosteroids to be given to children². Data on the safety of prolonged administration of inhaled corticosteroids in young children, particularly in terms of growth and pituitary-adrenal function, are therefore much needed. In previous studies with follow-up periods longer than one year in which the safety of inhaled corticosteroids in children was assessed,³⁻⁷ inhaled beclomethasone dipropionate was used in a dose of 300 to 400 μ g per day, and most of the patients evaluated were more than six years old. This report describes a long-term follow-up study of younger children with severe asthma treated with inhaled budesonide in whom the efficacy of the therapy and growth and pituitary-adrenal function were assessed repeatedly. The results demonstrate that the therapy was beneficial and safe, even for children treated for as long as five years.

METHODS

Patients

We studied 15 young children from our outpatient asthma clinic who had severe perennial asthma that was not controlled for a period of at least three months by continuous treatment with cromolyn sodium combined with terbutaline sulfate given either by nebulization or orally, sustained-release theophylline (given so that the patients' serum concentrations ranged from 10 to 20 μ g per milliliter), and occasional three-to-five-day courses of prednisone given orally. For these children, therefore, inhaled corticosteroid therapy seemed warranted.

At the beginning of the study no nebulized solution of budesonide was available.

However, since spacer devices allow children to be treated with inhaled budesonide, with

good clinical results,² we therefore chose these devices for dispensing budesonide supplied in metered-dose inhalers. The children had to be able to operate a spacer device, and preference was given to those capable of adequately measuring their peak expiratory flow rate with a meter.

Over 1000 children with asthma are followed in our clinic (including approximately 240 new patients every year). The 15 children studied entered the trial over a period of 15 months. These 15 children were all those followed in our outpatient clinic who received continuous treatment with budesonide for more than three years and who fulfilled the above criteria.

The budesonide was administered in two puffs twice daily, each puff containing 50 µg, for a total daily dose of 200 micrograms. During the first two years, a Nebuhaler (AB Draco, Lund, Sweden) was used; thereafter, a multispacer was substituted (Medic-aid, Sussex, United Kingdom) because it was considered easier for the young children to use.

The research protocol was reviewed and approved by the hospital's ethics committee for clinical investigation, and written informed consent was obtained from the parents of each child.

Study Design

Since a placebo-controlled trial was not feasible in these children because of the severity of their asthma, the study was an open trial. Budesonide therapy was started after a run-in period of one month. At the beginning of this period, cromolyn sodium therapy was discontinued. During this period, both terbutaline and theophylline were allowed but prednisone was not. A week after therapy with budesonide was begun, the parents were asked to discontinue the use of theophylline, but they could give terbutaline as needed. If an exacerbation of asthma occurred after budesonide therapy began, the parents were instructed to add terbutaline to the regimen if the child was not taking it, and then theophylline. If the asthma was severe, prednisone could be given for three to five days. After the second year of follow-up, an acute exacerbation of asthma was managed by a new treatment protocol that included a temporary increase in the dosage of budesonide, to 100 to 200 µg four times daily, preceded by two puffs of terbutaline. After one to three days, the dosage of inhaled budesonide was decreased to 100 µg three times daily, and one to three days later it was decreased to the maintenance dose of 100 µg twice daily. With this regimen almost all exacerbations of asthma were controlled with no need for prednisone.

Twice annually, at the end of each year of budesonide therapy and during the summer months (June through September), stopping budesonide therapy was proposed to the parents if the child's clinical condition would permit it.

The study began in February 1986. The children were examined monthly during the first year of treatment, and thereafter every three months.

Assessment of Clinical Response

The parents were asked to keep a daily record of the child's symptoms during the run-in period and then during the entire first year of budesonide therapy. Daily records were kept

thereafter only during exacerbations of asthma. From these records we determined the number of days on which the child had symptoms of asthma (diurnal and nocturnal cough, wheezing, and dyspnea), the use of bronchodilator drugs and prednisone, the daily peak expiratory flow rates (measured with a Mini Wright Peak Flow Meter [Clement Clarke International, London]), the number of days on which the child took an antibiotic drug for concurrent illnesses, and possible side effects.

At each visit we measured the peak expiratory flow rate and determined whether wheezing was present at the physical examination (a score of 0 was assigned if wheezing was absent, a score of 1 if it was mild, and a score of 2 if it was severe). The parents' and the physicians' opinions of the child's overall clinical condition were also recorded (scores ranged from 0, if asthma was absent, to 3, if it was severe). Compliance with budesonide administration was assessed by determining the ratio of the amount of drug remaining in the inhaler to the amount prescribed; the mean (\pm SD) ratio was 82 \pm 9 percent.

Assessment of Drug Safety

At each visit, a trained nurse measured the child's standing height with a stadiometer and his or her weight while the child wore minimal clothing. Weight, height, and height velocity were plotted on appropriate growth charts developed by Tanner et al⁸. Since the height velocity during the year before budesonide treatment was not known, we compared the height velocity during the later years of follow-up with that during the first year of follow-up. Bone age was determined at the start of the study and yearly thereafter from x-ray films of the left wrist, interpreted according to the radiographic atlas of Greulich and Pyle⁹. Pituitary-adrenal function was evaluated at the same time by measuring serum cortisol concentrations at 8 a.m. after an overnight fast and 60 minutes after intravenous administration of 0.25 mg of corticotropin (Cortrosyn, Organon International NV, Oss, the Netherlands). The morning dose of budesonide was given only after blood samples were obtained for the serum cortisol measurement.

Toward the end of the study we also measured serum cortisol concentrations in blood samples collected every 30 minutes for 24 hours and 24-hour urinary cortisol excretion in 11 of the 15 children (mean age, 9 years; range, 7 to 11). This group had been treated with budesonide for three to five years. Cortisol was measured while the children continued to take their usual twice-daily doses of budesonide. At the end of the study a slit-lamp eye examination was performed in all the children.

Cortisol Measurements

Serum and urinary cortisol concentrations were measured with commercial radioimmunoassay kits (Coat-A-Count, Diagnostic Products, Los Angeles). All samples from 24-hour studies of each child were analyzed at the same time. In normal children of comparable age, the fasting serum cortisol concentration at 8 a.m. ranged from 4 to 23 μ g per deciliter (110 to 635 nmol per liter) in our laboratory, the serum cortisol 60 minutes after corticotropin administration ranged from 18 to 50 μ g per deciliter (497 to 1380 nmol per liter), and the mean 24-hour urinary cortisol excretion ranged from 12 to 55 μ g per day (33 to 152 nmol per day). The interassay and intraassay coefficients of variation for serum

cortisol concentrations ranged from 4.5 to 6.5 percent and from 3 to 8 percent, respectively.

Statistical Analysis

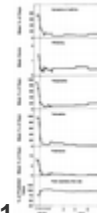
The results during budesonide therapy were compared with those during the three-month period preceding the beginning of the one-month run-in period, or with those during the run-in period before the initiation of budesonide therapy. Values are expressed as means ±SD. Differences within groups were compared by paired t-tests. All tests were two-tailed, and P values below 0.05 were considered to indicate statistical significance.

RESULTS

The 15 children -- 10 boys and 5 girls, 2 to 7 years old at the start of the study (mean, 4 years 10 months) -- were followed for at least 3 and as long as 5 years (mean ±SD, 4 ±1). During this period, most of them received budesonide continuously in a dose of 100 µg twice daily. After four years of treatment, three children (9, 10, and 11 years old) required a dose of 150 µg twice daily.

Clinical Response

As compared with the control of asthma during the one-month run-in period of severe asthma immediately before the start of budesonide therapy, control improved during the first month after the beginning of therapy. During this month, there was a 58 percent decrease in the number of days with symptoms of asthma, a 75 percent decrease in the use of terbutaline, theophylline, and prednisone, a 71 percent decrease in the score for wheezing, and a 17 percent increase in the mean peak expiratory flow rate (in the 12



children who were capable of using a flow meter correctly) (Figure 1). Changes in Asthmatic Status before and during Inhaled Budesonide Therapy in 15 Children with Severe Asthma. The improvement was maintained throughout the period of treatment. There was also a large decrease in the number of exacerbations of asthma, the number of visits to the emergency room, and the number of hospitalizations (Table

Parameter	n	Mean (SD)				
		Run-in	1st mo	3 mo	1 yr	2 yr
Days with symptoms	15	12.5 (4.5)	3.8 (1.5)	3.5 (1.5)	3.2 (1.5)	3.1 (1.5)
Days with wheezing	15	10.5 (4.5)	3.2 (1.5)	3.0 (1.5)	2.8 (1.5)	2.7 (1.5)
Days with cough	15	11.5 (4.5)	3.5 (1.5)	3.2 (1.5)	3.0 (1.5)	2.9 (1.5)
Days with chest tightness	15	10.5 (4.5)	3.2 (1.5)	3.0 (1.5)	2.8 (1.5)	2.7 (1.5)
Days with shortness of breath	15	11.5 (4.5)	3.5 (1.5)	3.2 (1.5)	3.0 (1.5)	2.9 (1.5)
Days with asthma attacks	15	12.5 (4.5)	3.8 (1.5)	3.5 (1.5)	3.2 (1.5)	3.1 (1.5)
Days with hospitalizations	15	13.5 (4.5)	4.2 (1.5)	4.0 (1.5)	3.8 (1.5)	3.7 (1.5)
Days with emergency room visits	15	14.5 (4.5)	4.5 (1.5)	4.2 (1.5)	4.0 (1.5)	3.9 (1.5)
Days with antibiotic use	15	15.5 (4.5)	4.2 (1.5)	4.0 (1.5)	3.8 (1.5)	3.7 (1.5)
Days with steroid use	15	16.5 (4.5)	4.5 (1.5)	4.2 (1.5)	4.0 (1.5)	3.9 (1.5)
Days with theophylline use	15	17.5 (4.5)	4.8 (1.5)	4.5 (1.5)	4.2 (1.5)	4.1 (1.5)
Days with terbutaline use	15	18.5 (4.5)	5.2 (1.5)	4.8 (1.5)	4.5 (1.5)	4.4 (1.5)
Days with beta-2 agonist use	15	19.5 (4.5)	5.5 (1.5)	5.2 (1.5)	4.8 (1.5)	4.7 (1.5)
Days with inhaled corticosteroid use	15	20.5 (4.5)	5.8 (1.5)	5.5 (1.5)	5.2 (1.5)	5.1 (1.5)
Days with oral corticosteroid use	15	21.5 (4.5)	6.2 (1.5)	5.8 (1.5)	5.5 (1.5)	5.4 (1.5)
Days with systemic steroid use	15	22.5 (4.5)	6.5 (1.5)	6.2 (1.5)	5.8 (1.5)	5.7 (1.5)
Days with oral antibiotic use	15	23.5 (4.5)	6.8 (1.5)	6.5 (1.5)	6.2 (1.5)	6.1 (1.5)
Days with systemic antibiotic use	15	24.5 (4.5)	7.2 (1.5)	6.8 (1.5)	6.5 (1.5)	6.4 (1.5)
Days with hospitalization	15	25.5 (4.5)	7.5 (1.5)	7.2 (1.5)	6.8 (1.5)	6.7 (1.5)
Days with emergency room visit	15	26.5 (4.5)	7.8 (1.5)	7.5 (1.5)	7.2 (1.5)	7.1 (1.5)
Days with asthma attack	15	27.5 (4.5)	8.2 (1.5)	7.8 (1.5)	7.5 (1.5)	7.4 (1.5)
Days with wheezing	15	28.5 (4.5)	8.5 (1.5)	8.2 (1.5)	7.8 (1.5)	7.7 (1.5)
Days with cough	15	29.5 (4.5)	8.8 (1.5)	8.5 (1.5)	8.2 (1.5)	8.1 (1.5)
Days with chest tightness	15	30.5 (4.5)	9.2 (1.5)	8.8 (1.5)	8.5 (1.5)	8.4 (1.5)
Days with shortness of breath	15	31.5 (4.5)	9.5 (1.5)	9.2 (1.5)	8.8 (1.5)	8.7 (1.5)
Days with asthma symptoms	15	32.5 (4.5)	9.8 (1.5)	9.5 (1.5)	9.2 (1.5)	9.1 (1.5)
Days with asthma exacerbation	15	33.5 (4.5)	10.2 (1.5)	9.8 (1.5)	9.5 (1.5)	9.4 (1.5)
Days with asthma flare-up	15	34.5 (4.5)	10.5 (1.5)	10.2 (1.5)	9.8 (1.5)	9.7 (1.5)
Days with asthma attack	15	35.5 (4.5)	10.8 (1.5)	10.5 (1.5)	10.2 (1.5)	10.1 (1.5)
Days with asthma episode	15	36.5 (4.5)	11.2 (1.5)	10.8 (1.5)	10.5 (1.5)	10.4 (1.5)
Days with asthma event	15	37.5 (4.5)	11.5 (1.5)	11.2 (1.5)	10.8 (1.5)	10.7 (1.5)
Days with asthma incident	15	38.5 (4.5)	11.8 (1.5)	11.5 (1.5)	11.2 (1.5)	11.1 (1.5)
Days with asthma occurrence	15	39.5 (4.5)	12.2 (1.5)	11.8 (1.5)	11.5 (1.5)	11.4 (1.5)
Days with asthma manifestation	15	40.5 (4.5)	12.5 (1.5)	12.2 (1.5)	11.8 (1.5)	11.7 (1.5)
Days with asthma presentation	15	41.5 (4.5)	12.8 (1.5)	12.5 (1.5)	12.2 (1.5)	12.1 (1.5)
Days with asthma expression	15	42.5 (4.5)	13.2 (1.5)	12.8 (1.5)	12.5 (1.5)	12.4 (1.5)
Days with asthma appearance	15	43.5 (4.5)	13.5 (1.5)	13.2 (1.5)	12.8 (1.5)	12.7 (1.5)
Days with asthma development	15	44.5 (4.5)	13.8 (1.5)	13.5 (1.5)	13.2 (1.5)	13.1 (1.5)
Days with asthma growth	15	45.5 (4.5)	14.2 (1.5)	13.8 (1.5)	13.5 (1.5)	13.4 (1.5)
Days with asthma expansion	15	46.5 (4.5)	14.5 (1.5)	14.2 (1.5)	13.8 (1.5)	13.7 (1.5)
Days with asthma increase	15	47.5 (4.5)	14.8 (1.5)	14.5 (1.5)	14.2 (1.5)	14.1 (1.5)
Days with asthma improvement	15	48.5 (4.5)	15.2 (1.5)	14.8 (1.5)	14.5 (1.5)	14.4 (1.5)
Days with asthma recovery	15	49.5 (4.5)	15.5 (1.5)	15.2 (1.5)	14.8 (1.5)	14.7 (1.5)
Days with asthma relief	15	50.5 (4.5)	15.8 (1.5)	15.5 (1.5)	15.2 (1.5)	15.1 (1.5)
Days with asthma resolution	15	51.5 (4.5)	16.2 (1.5)	15.8 (1.5)	15.5 (1.5)	15.4 (1.5)
Days with asthma cessation	15	52.5 (4.5)	16.5 (1.5)	16.2 (1.5)	15.8 (1.5)	15.7 (1.5)
Days with asthma termination	15	53.5 (4.5)	16.8 (1.5)	16.5 (1.5)	16.2 (1.5)	16.1 (1.5)
Days with asthma completion	15	54.5 (4.5)	17.2 (1.5)	16.8 (1.5)	16.5 (1.5)	16.4 (1.5)
Days with asthma fulfillment	15	55.5 (4.5)	17.5 (1.5)	17.2 (1.5)	16.8 (1.5)	16.7 (1.5)
Days with asthma realization	15	56.5 (4.5)	17.8 (1.5)	17.5 (1.5)	17.2 (1.5)	17.1 (1.5)
Days with asthma attainment	15	57.5 (4.5)	18.2 (1.5)	17.8 (1.5)	17.5 (1.5)	17.4 (1.5)
Days with asthma achievement	15	58.5 (4.5)	18.5 (1.5)	18.2 (1.5)	17.8 (1.5)	17.7 (1.5)
Days with asthma accomplishment	15	59.5 (4.5)	18.8 (1.5)	18.5 (1.5)	18.2 (1.5)	18.1 (1.5)
Days with asthma success	15	60.5 (4.5)	19.2 (1.5)	18.8 (1.5)	18.5 (1.5)	18.4 (1.5)
Days with asthma completion	15	61.5 (4.5)	19.5 (1.5)	19.2 (1.5)	18.8 (1.5)	18.7 (1.5)
Days with asthma fulfillment	15	62.5 (4.5)	19.8 (1.5)	19.5 (1.5)	19.2 (1.5)	19.1 (1.5)
Days with asthma realization	15	63.5 (4.5)	20.2 (1.5)	19.8 (1.5)	19.5 (1.5)	19.4 (1.5)
Days with asthma attainment	15	64.5 (4.5)	20.5 (1.5)	20.2 (1.5)	19.8 (1.5)	19.7 (1.5)
Days with asthma achievement	15	65.5 (4.5)	20.8 (1.5)	20.5 (1.5)	20.2 (1.5)	20.1 (1.5)
Days with asthma accomplishment	15	66.5 (4.5)	21.2 (1.5)	20.8 (1.5)	20.5 (1.5)	20.4 (1.5)
Days with asthma success	15	67.5 (4.5)	21.5 (1.5)	21.2 (1.5)	20.8 (1.5)	20.7 (1.5)
Days with asthma completion	15	68.5 (4.5)	21.8 (1.5)	21.5 (1.5)	21.2 (1.5)	21.1 (1.5)
Days with asthma fulfillment	15	69.5 (4.5)	22.2 (1.5)	21.8 (1.5)	21.5 (1.5)	21.4 (1.5)
Days with asthma realization	15	70.5 (4.5)	22.5 (1.5)	22.2 (1.5)	21.8 (1.5)	21.7 (1.5)
Days with asthma attainment	15	71.5 (4.5)	22.8 (1.5)	22.5 (1.5)	22.2 (1.5)	22.1 (1.5)
Days with asthma achievement	15	72.5 (4.5)	23.2 (1.5)	22.8 (1.5)	22.5 (1.5)	22.4 (1.5)
Days with asthma accomplishment	15	73.5 (4.5)	23.5 (1.5)	23.2 (1.5)	22.8 (1.5)	22.7 (1.5)
Days with asthma success	15	74.5 (4.5)	23.8 (1.5)	23.5 (1.5)	23.2 (1.5)	23.1 (1.5)
Days with asthma completion	15	75.5 (4.5)	24.2 (1.5)	23.8 (1.5)	23.5 (1.5)	23.4 (1.5)
Days with asthma fulfillment	15	76.5 (4.5)	24.5 (1.5)	24.2 (1.5)	23.8 (1.5)	23.7 (1.5)
Days with asthma realization	15	77.5 (4.5)	24.8 (1.5)	24.5 (1.5)	24.2 (1.5)	24.1 (1.5)
Days with asthma attainment	15	78.5 (4.5)	25.2 (1.5)	24.8 (1.5)	24.5 (1.5)	24.4 (1.5)
Days with asthma achievement	15	79.5 (4.5)	25.5 (1.5)	25.2 (1.5)	24.8 (1.5)	24.7 (1.5)
Days with asthma accomplishment	15	80.5 (4.5)	25.8 (1.5)	25.5 (1.5)	25.2 (1.5)	25.1 (1.5)

TABLE 1 Control of Asthma in Children Treated with Budesonide. Both

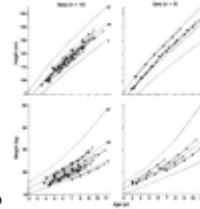
the parents and the physicians noted substantial overall improvement in the control of asthma. The number of days during which the children took an antibiotic drug decreased by 73 percent (Table 1). During the entire study period, six children did not need any antibiotic treatment for concurrent illnesses and four took antibiotics on only one occasion. During the entire treatment period, discontinuation of budesonide therapy was attempted on 46 occasions in all 15 children, but the drug could be discontinued in only 2 of them (after four years of treatment). All other attempts were followed by a recurrence of

symptoms. Forty of the 44 unsuccessful attempts (91 percent) failed within 2 to 30 days (mean, 14) after budesonide was discontinued.

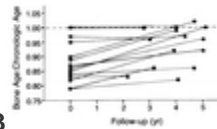
Assessment of Drug Safety

Linear Growth

Before budesonide therapy began, the height and weight of the children were within the



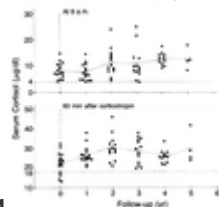
normal ranges for their ages (Figure 2). Changes in Height and Weight during Inhaled Budesonide Therapy. In contrast, their bone age was less than their



chronologic age (Figure 3). Changes in the Ratio of Bone Age to Chronologic Age during Budesonide Therapy. During therapy all the children grew and gained weight according to their height and weight percentiles (Figure 2). Their height velocity during the first year of therapy, which was in the 60th (± 23) percentile for normal children, did not change thereafter (mean percentile, 66 ± 17). Their bone age advanced in parallel with their chronologic age (Figure 3).

Adrenal Function

During budesonide therapy, all children had normal fasting (8 a.m.) serum cortisol concentrations (mean, $10.6 \pm 4.3 \mu\text{g}$ per deciliter [$292 \pm 119 \text{ nmol}$ per liter]) and normal serum cortisol responses to corticotropin (mean concentration 60 minutes after the administration of corticotropin, $28.1 \pm 5.6 \mu\text{g}$ per deciliter [$774 \pm 155 \text{ nmol}$ per liter]) (Figure



4). Changes in Serum Cortisol Concentrations during Budesonide Therapy. The 24-hour serum cortisol concentration, calculated as the average of values measured every 30 minutes for 24 hours in the 11 children in whom this variable was measured, was $8.4 \pm 4.2 \mu\text{g}$ per deciliter ($232 \pm 116 \text{ nmol}$ per liter); there were several peaks during the day, and concentrations were highest in the early morning, as reported in normal children and in children with asthma who had not received inhaled corticosteroid therapy¹⁰. The mean 24-hour urinary cortisol excretion was normal in these 11 children ($34 \pm 9 \mu\text{g}$ [$95 \pm 25 \text{ nmol}$] per day; range, 24 to $53 \mu\text{g}$ [66 to 146 nmol]).

Other Studies

Slit-lamp eye examinations did not reveal any cataract formation. One child had dysphonia for three days at the beginning of treatment. No other side effects, including oral candidiasis, were reported.

DISCUSSION

Budesonide is a nonhalogenated corticosteroid with high topical antiinflammatory potency and low systemic bioavailability^{11,12}. The prolonged administration of budesonide to children with asthma led to an improvement in airway hyperresponsiveness accompanied by clinical control of asthma¹³⁻¹⁵.

The results of this study confirm the long-term efficacy of inhaled budesonide in young children, albeit in an uncontrolled study, and in addition demonstrate that the treatment does not impair growth or inhibit pituitary-adrenal function. In the selected children with severe asthma whom we studied, treatment with a relatively low dose of budesonide was associated with an excellent clinical response, beginning soon after the initiation of treatment and lasting throughout the follow-up period. Budesonide therapy was necessary to control asthma during the follow-up period, because its discontinuation in the 15 children (46 attempts) resulted in a recurrence of asthma in all but 2 children.

The most important safety consideration in young children treated with inhaled corticosteroids for long periods is the effect of the treatment on their growth and pituitary-adrenal function. The adverse effects of inhaled corticosteroid therapy are dose-dependent¹⁶⁻¹⁸. Treatment with beclomethasone in a dose of 300 to 600 µg per day for more than one year did not adversely affect the final height of the children³⁻⁷. Similarly, most children treated with budesonide for a year grew normally^{14,15,19}. There may, however, be some slowing of linear growth, especially when relatively high doses of inhaled corticosteroids are used. For example, children given 800 µg of budesonide per day for 12 weeks had a decrease in linear growth, whereas those treated with 200 or 400 µg per day did not^{16,17}. In another study, treatment with 200 to 800 µg of beclomethasone per day had an adverse effect on growth²⁰. However, the impairment of growth in the children in that study might have been due to physiologic deceleration of their growth rate or, in the older children, to a delay of the onset of puberty, which has been reported in children with asthma^{3,21,22}. In our study, the linear growth of the children was normal for their age at all times. Their bone age was slightly delayed before they received budesonide, but this delay in bone age was shortened slightly during treatment. With respect to another skeletal complication of corticosteroid therapy -- bone disease -- in a recent study in children, inhaled beclomethasone in doses up to 800 µg per day had no effect on bone mineralization or bone resorption²³.

In several long-term studies of children with asthma treated with beclomethasone or budesonide in doses up to 800 mg per day, pituitary-adrenal function was normal as reflected by normal base-line serum cortisol concentrations,^{7,24} normal serum cortisol responses to corticotropin,^{5,7,24} and normal 24-hour urinary excretion of cortisol^{24,25}. However, other studies of beclomethasone, given in doses of 400 to 800 µg per day, found some evidence of adrenal suppression -- most often, decreased urinary cortisol excretion^{10,26-30}. Treatment with higher doses (1000 to 1800 µg per day) of either corticosteroid usually caused adrenal suppression^{18,29}. In our study, the results of all tests of pituitary-adrenal function were normal at all times, indicating the absence of

pituitary or adrenal suppression, but unfortunately not all the tests were carried out before budesonide therapy was started.

Giving patients with asthma inhaled corticosteroids predisposes them to colonization of the oropharynx with *Candida albicans*[7,31](#). This colonization and the dysphonia that may accompany it are often related to the dose of the corticosteroid and the frequency of its administration[32-34](#). The occurrence of this side effect is usually reduced by using spacer devices, which reduce the amount of corticosteroid deposited in the oropharynx[35](#). Our use of a spacer and lower doses of budesonide could account for the absence of oral candidiasis in any of the children studied.

Treatment with oral corticosteroids may induce the formation of posterior subcapsular cataracts[36](#). The formation of a cataract in a child treated with inhaled budesonide has been reported, although the child had also received short courses of oral corticosteroid therapy[37](#). No cataracts were found in any of our patients.

We conclude that prolonged administration of inhaled budesonide in a relatively low dose of 200 µg per day to young children with severe asthma is not only effective but also safe, as demonstrated by their normal linear growth and normal pituitary-adrenal function.

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SOURCE INFORMATION

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