

Efficacy of budesonide inhalation suspension in infants and young children with persistent asthma

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This paper reviews the results from 3 randomized, double-blind, placebo-controlled, multicenter studies that assessed the efficacy and safety of once- and twice-daily dosing of budesonide inhalation suspension (BIS) in infants and young children with persistent asthma. In children with mild persistent asthma that was previously treated with bronchodilators or noncorticosteroid anti-inflammatory agents (study A), nighttime and daytime asthma symptoms were significantly improved in 0.25-mg once daily, 0.5-mg once daily, and 1.0-mg once daily BIS treatment groups compared with placebo ($P \leq .05$). Rescue medications were used significantly less in all BIS groups (approximately 2 days of every 14 days) compared with placebo ($P < .05$). The proportion of patients who discontinued this therapy because of worsening asthma was greater in the placebo group than in the BIS groups, with the difference between placebo (23%) and the 1.0-mg BIS group (13%) being statistically significant ($P = .020$). All BIS doses except 0.5 mg once daily showed nonsignificant numeric improvement in morning and evening peak expiratory flow (PEF) compared with placebo. In children with asthma that was previously treated with inhaled corticosteroids (study B), BIS doses of 0.25 mg, 0.5 mg, and 1.0 mg twice daily resulted in significant improvements in nighttime symptoms scores versus placebo ($P \leq .026$). Rescue medications were used significantly less in all BIS groups (approximately 2.5 to 3.5 days of every 14 days) compared with placebo ($P \leq .032$). The proportion of patients receiving placebo who discontinued therapy because of worsening asthma symptoms (36%) was significantly greater compared with the BIS groups (9%; $P \leq .015$). Morning PEF levels were significantly greater in each BIS group compared with placebo ($P \leq .03$). For evening PEF levels, all BIS treatment groups showed numeric improvements compared with placebo; the 0.25-mg twice daily budesonide group showed statistically significant improvement ($P < .05$). In children with moderate persistent asthma that was previously maintained either on bronchodilators or inhaled corticosteroids (study C), nighttime asthma symptoms significantly improved in the 0.25-mg twice daily, 0.5-mg twice daily, and 1.0-mg once daily BIS groups compared with placebo ($P < .01$); there was a numeric improvement for the 0.25-mg once daily treatment group. Rescue medications were used significantly less in all BIS groups (approximately 2 to 3 days of every 14 days) compared with placebo ($P \leq .014$). The proportion of patients who discontinued treatment because of worsening of asthma symptoms was greater in the placebo group than in the BIS groups; the difference between 0.25-mg twice daily group (13%) and the

placebo group (26%) was statistically significant ($P = .029$). All BIS doses showed numeric improvement in morning PEF levels, and statistically significant improvements were observed in the 0.25-mg twice daily, 0.5-mg twice daily, and 1.0-mg once daily groups compared with placebo ($P < .03$). Significant improvements in evening PEF levels were observed for each BIS treatment group ($P \leq .034$), except for the 1.0-mg once daily group. Overall, the 3 studies show that once- and twice-daily dosing of BIS effectively relieves asthma symptoms and improves pulmonary function in infants and young children with mild-to-severe persistent asthma. (*J Allergy Clin Immunol* 1999;104:S191-9)

Key words: Budesonide, budesonide inhalation suspension, asthma, corticosteroid, pediatric, efficacy, pulmonary function

Inhaled corticosteroids are the most potent and consistently effective medications for long-term control of asthma, and the most recent asthma guidelines from the National Asthma Education and Prevention Program recommend their use for the treatment of persistent asthma in children 5 years of age and younger.¹ Studies indicate that early intervention with inhaled corticosteroids may be critical in the long-term preservation of pulmonary function and may prevent irreversible airway obstruction, airway remodeling, and hyperresponsiveness.²⁻⁴

Unfortunately, many children may not be able to use some inhalation devices (eg, metered-dose inhalers with or without a spacer and inhalation-driven dry powder inhalers) correctly because of a lack of coordination and understanding of the devices,⁵ negating the full benefit from the inhaled medication.⁶ In very young children or older children unable to properly use these devices, tidal breathing is primarily used to achieve effective drug delivery, limiting delivery systems to nebulizers and holding chambers with face masks.⁷ An advantage of nebulization as a delivery method for inhaled corticosteroids is that it depends less on patient coordination or cooperation, which is particularly important in children younger than 2 years of age.¹ Hence nebulizer therapy may be the preferred route of administration in young children and older children who are unable to master the technique with other devices.⁸⁻¹⁰

Budesonide inhalation suspension (BIS; Pulmicort RespulesTM; AstraZeneca, Wayne, Pa), given by nebulizer, has been developed to address the needs of infants and young children who require inhaled corticosteroids; it is easily delivered because it does not require coordination or active deep inhalation. BIS will be the first inhaled corticosteroid approved for use in the United States in a nebulizer for pediatric patients and the first inhaled corti-

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TABLE I. Asthma history, baseline symptom scores, and baseline pulmonary function data¹⁸⁻²⁰

	Study A*				Study B†				Study C‡				
	Placebo	BIS (mg)			Placebo	BIS (mg)			Placebo	BIS (mg)			
		0.25 QD	0.5 QD	1.0 QD		0.25 BID	0.5 BID	1.0 BID		0.25 QD	0.25 BID	0.5 BID	1.0 QD
N	92	91	83	93	44	47	42	45	95	94	99	98	95
Duration of asthma (mo)													
Mean±SD	37.1	35.4	36.7	36.1	49.8	51.8	48.1	53.1	35.6	34.2	32.4	33.3	35.4
	±22	±22	±25	±24	±27	±21	±23	±19	±23	±23	±23	±23	±24
Range	5-92	5-97	5-107	5-107	6-102	13-92	6-94	11-100	5-90	2-92	4-96	4-88	6-98
Nighttime asthma symptom scores§ (mean)	1.08	1.32	1.19	1.19	1.18	1.10	1.04	1.08	1.16	1.13	1.33	1.20	1.25
Daytime asthma symptom scores§ (mean)	1.27	1.44	1.33	1.31	1.33	1.35	1.33	1.35	1.27	1.21	1.31	1.33	1.28
Morning PEF (L/min)													
N	55	44	41	55	44	47	42	45	32	32	34	29	34
Mean	150.7	151.5	149.2	136.9	158.3	155.6	162.1	160.8	155.8	164.2	157.1	166.9	156.6
Evening PEF (L/min)													
N	55	42	41	54	44	47	42	45	32	32	34	29	34
Mean	143.9	142.4	137.5	130.8	164.7	160.9	171.6	169.9	160.8	169.9	168.7	176.7	166.2
FEV ₁													
N	38	29	28	33	44	47	42	45	31	33	34	30	35
% Predicted	81.6	83.8	81.9	78.3	79.2	80.5	78.8	80.2	79.1	78.7	83.1	79.8	78.3
N	39	29	29	33	44	47	42	45	32	33	34	30	36
% Reversibility	27.0	26.1	31.6	26.3	30.3	35.9	36.2	32.3	29.1	28.9	30.5	30.5	26.9

BID, Twice daily; QD, once daily.

*Patients whose asthma was not controlled with bronchodilator or noncorticosteroid anti-inflammatory agents.

†Patients whose asthma was treated with inhaled corticosteroids.

‡Patients whose asthma was treated with bronchodilator or inhaled corticosteroids.

§Symptom scoring scale of 0 to 3 (0, no symptoms; 1, mild symptoms; 2, moderate symptoms; 3, severe symptoms).

Abbreviations used

BIS: Budesonide inhalation suspension
PEF: Peak expiratory flow

corticosteroid for children less than 4 years of age in the United States. The development of BIS is an important advance over previously available therapies because it will allow physicians to institute inhaled corticosteroids at an earlier age (which may prevent irreversible airway remodeling) and to avoid the use of systemic corticosteroids. Early trials and individual case studies reported BIS to be effective in reducing asthma symptoms in infants and children.¹¹⁻¹⁷ More recently, the therapeutic efficacy of BIS has been evaluated in 3 pivotal clinical trials involving more than 1000 pediatric patients (6 months to 8 years of age) with persistent asthma of varying disease duration (2 to 107 months) and severity.

This article reviews the efficacy results of these 3 randomized, placebo-controlled, double-blind studies.¹⁸⁻²⁰ Study A was designed to evaluate once-daily administration of BIS in children (6 months to 8 years of age) with mild persistent asthma that was treated with bronchodilators or noncorticosteroid anti-inflammatory agents.¹⁹ Study B evaluated twice daily administration of

BIS in children (4 to 8 years of age) with moderate-to-severe persistent asthma that was treated with inhaled corticosteroids.²⁰ Study C evaluated once- or twice-daily dosing of BIS in children (6 months to 8 years of age) with moderate persistent asthma that was treated with either bronchodilators or inhaled corticosteroids.¹⁸

The methods for each study have been described in detail by Kemp in this issue ("Study Designs and Challenges in Clinical Studies Conducted in Infants and Children with Asthma"). Briefly, all 3 studies used nighttime and daytime asthma symptom scores as primary efficacy variables. Subjective measures of asthma symptoms were used because of the difficulty of obtaining uniform pulmonary function tests in children under 4 years of age.^{1,5,21-24} In addition, clinical scoring systems are commonly used as the sole measures to diagnose asthma and for primary efficacy assessment in clinical trials for other asthma medications,²⁵ making comparisons between studies possible. Secondary measures of efficacy included the number of days medication was required for breakthrough asthma symptoms, patient discontinuation of therapy (overall and asthma symptom-related), and pulmonary function tests. Pulmonary function tests were conducted in the subset of patients who were able to perform them and included morning and evening peak expiratory flow (PEF; liters per minute) and FEV₁ (liters per minute) levels. Effi-

cacy analyses included all patients who received at least 1 study medication dose and had at least 1 observation taken while receiving study medication.

ASTHMA HISTORY AND BASELINE ASTHMA SEVERITY

A detailed description of patient demographics for the double-blind studies is provided by Kemp ("Study Designs and Challenges in Clinical Studies Conducted in Infants and Children with Asthma") in this issue. Asthma history, baseline nighttime and daytime symptom scores, and baseline pulmonary function data for studies A, B, and C are shown in Table I. Within each study, treatment groups were comparable with regard to baseline nighttime and daytime asthma symptoms, morning and evening PEF levels, and FEV₁.

Study A consisted of patients whose asthma was previously treated with bronchodilators and noncorticosteroid anti-inflammatory agents. Asthma medications most frequently used within 90 days before enrollment were oral and inhaled albuterol (>99%), cromolyn sodium (76%), and prednisolone bursts (19%); patients who used inhaled corticosteroids were excluded from the study. Most treatment groups were comparable with regard to baseline nighttime and daytime asthma symptoms, except for the 0.25-mg BIS group, which had slightly higher baseline scores. Overall, the mean baseline nighttime asthma symptom score was 1.19 ± 0.63 , and the mean baseline daytime asthma symptom score was 1.34 ± 0.53 . Approximately 55% of randomized patients were able to perform PEF, and approximately 36% of these patients were able to perform spirometry consistently. Mean morning and evening PEF levels were similar, and mean baseline FEV₁ was 81.3% of predicted, with 27.7% reversibility. Rescue medication (inhaled albuterol) was required during the 2-week baseline period on a mean of 10.8, 11.6, 11.3, and 10.6 days in the placebo, 0.25-mg once daily, 0.5-mg once daily, and 1.0-mg once daily BIS treatment groups, respectively.

Study B consisted of patients whose asthma was previously treated with inhaled corticosteroids; before randomization, beclomethasone (59%) was the most frequently used inhaled corticosteroid. The mean nighttime and daytime baseline asthma symptom scores at baseline were 1.10 ± 0.59 and 1.34 ± 0.50 , respectively. Pulmonary function tests were performed by all patients in this study and were similar across the 4 treatment groups at baseline (Table I). Mean morning and evening PEF levels were similar, and mean baseline FEV₁ was 79.7% of predicted, with 33.7% reversibility. Rescue medication was required during the 2-week baseline period on a mean of 11.8, 11.6, 12.0, and 10.8 days in placebo, 0.25-mg twice daily, 0.5-mg twice daily, and 1.0-mg twice daily BIS treatment groups, respectively.

In study C, asthma medications most frequently used at the time of randomization were oral and inhaled albuterol (>99%), cromolyn sodium (72%), inhaled corticosteroids (31%), and theophylline (10%). The mean duration of asthma was 34.2 months (range, 2-98

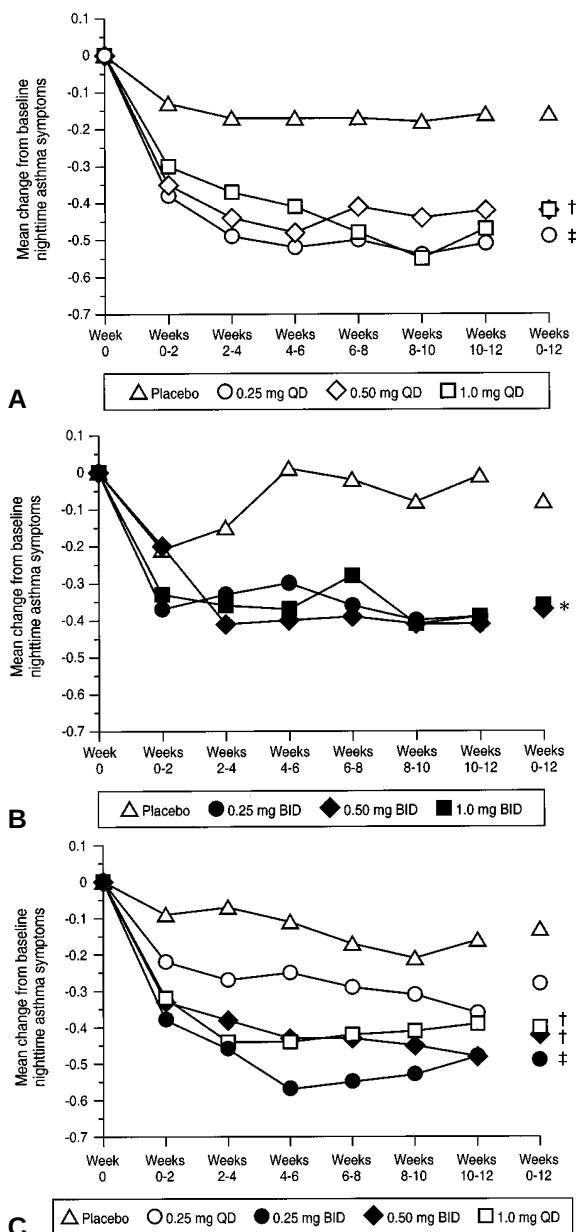


FIG 1. Mean change from baseline in nighttime asthma symptom scores over 12 weeks of double-blind treatment. **A**, Patients whose asthma was not previously controlled with bronchodilators or noncorticosteroid anti-inflammatory agents. (From Kemp JP, Skoner D, Szefer SJ, Walton-Bowen K, Cruz-Rivera M, Smith JA. Once-daily budesonide inhalation suspension for the treatment of persistent asthma in infants and young children. *Ann Allergy Asthma Immunol* 1999;83:231-9. By permission.) **B**, Patients whose asthma was previously treated with inhaled corticosteroids. (From Shapiro G, Mendelson L, Kraemer MJ, Cruz-Rivera M, Walton-Bowen K, Smith JA. Efficacy and safety of budesonide inhalation suspension [Pulmicort Respules] in young children with inhaled steroid-dependent, persistent asthma. *J Allergy Clin Immunol* 1998;102:789-96. By permission.) **C**, Patients whose asthma was previously treated with either bronchodilators or inhaled corticosteroids. (From Baker J, Mellon M, Wald J, Welch M, Cruz-Rivera M, Walton-Bowen K. A multiple-dosing, placebo-controlled study of budesonide nebulizing suspension given once or twice daily for treatment of persistent asthma in young children and infants. *Pediatrics* 1999;103:414-21. Reproduced by permission of Pediatrics.) * $P \leq .05$, † $P \leq .01$, ‡ $P \leq .001$ versus placebo.

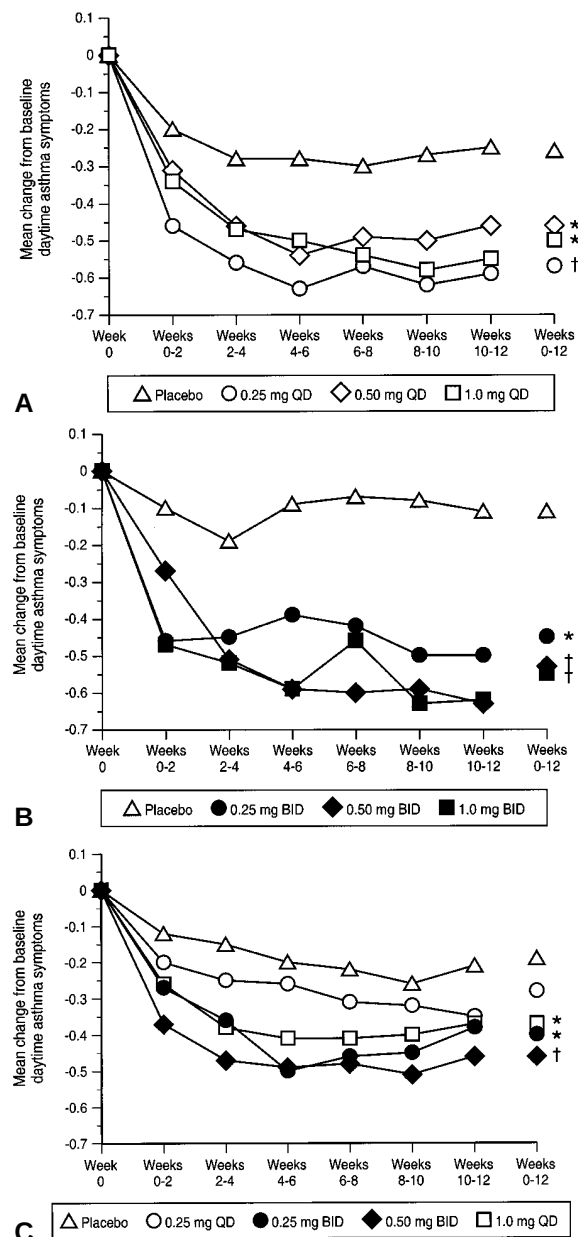


FIG 2. Mean change from baseline in daytime asthma symptom scores over 12 weeks of double-blind treatment. **A**, Patients whose asthma was not previously controlled with bronchodilators or non-corticosteroid anti-inflammatory agents. (From Kemp JP, Skoner D, Szefer SJ, Walton-Bowen K, Cruz-Rivera M, Smith JA. Once-daily budesonide inhalation suspension for the treatment of persistent asthma in infants and young children. *Ann Allergy Asthma Immunol* 1999;83:231-9. By permission.) **B**, Patients whose asthma was previously treated with inhaled corticosteroids. (From Shapiro G, Mendelson L, Kraemer MJ, Cruz-Rivera M, Walton-Bowen K, Smith JA. Efficacy and safety of budesonide inhalation suspension [Pulmicort Respules] in young children with inhaled steroid-dependent, persistent asthma. *J Allergy Clin Immunol* 1998;102:789-96. By permission.) **C**, Patients whose asthma was previously treated with either bronchodilators or inhaled corticosteroids. (From Baker J, Mellon M, Wald J, Welch M, Cruz-Rivera M, Walton-Bowen K. A multiple-dosing, placebo-controlled study of budesonide nebulizing suspension given once or twice daily for treatment of persistent asthma in young children and infants. *Pediatrics* 1999;103:414-21. Reproduced by permission of Pediatrics.) * $P \leq .05$, † $P \leq .01$, ‡ $P \leq .001$ versus placebo.

months); the mean baseline nighttime asthma symptom score was 1.22 ± 0.62 , and the mean baseline daytime asthma symptom score was 1.28 ± 0.50 . As shown in Table I, pulmonary function tests at baseline were similar across treatment groups. In patients who were capable of performing pulmonary function tests (34% of all patients), mean morning and evening PEF levels were similar, and mean baseline FEV₁ was 79.8% of predicted, with 29.1% reversibility. Rescue medication was required during the 2-week baseline period on a mean of 7.26, 8.73, 9.01, 8.10, and 8.35 days in placebo, 0.25-mg once daily, 0.25-mg twice daily, 0.5-mg twice daily, and 1.0-mg once daily BIS treatment groups, respectively.

CLINICAL EFFICACY

Nighttime and daytime asthma symptoms

Mean changes from baseline in nighttime asthma symptom scores over the 12-week treatment period in patients whose asthma was previously treated with bronchodilators and/or noncorticosteroid anti-inflammatory agents (study A), in patients whose asthma was treated with inhaled corticosteroids (study B), and in patients whose asthma was treated with either bronchodilators or inhaled corticosteroids (study C) are shown in Fig 1. Overall, for each patient population and treatment dose, improvements in nighttime asthma symptoms were evident within 2 to 5 days after therapy was initiated. The observed reduction in symptoms was sustained throughout the 12-week, double-blind treatment phase.

In study A, at the end of 12 weeks of treatment, nighttime asthma symptoms were significantly improved in 0.25-mg once daily, 0.5-mg once daily, and 1.0-mg once daily BIS treatment groups compared with placebo ($P \leq .05$). In study B, BIS doses of 0.25-mg twice daily, 0.5-mg twice daily, and 1.0-mg twice daily resulted in significant improvements in nighttime symptom scores ($P \leq .026$ versus placebo). In study C, mean changes from baseline to 12 weeks for nighttime asthma symptoms in patients in the 0.25-mg twice daily, 0.5-mg twice daily, and 1.0-mg once daily BIS treatment groups were significantly greater compared with placebo ($P < .01$); there was a numeric improvement for the 0.25-mg once daily treatment group.

Similar results were observed across the 12-week treatment period for daytime asthma symptoms (Fig 2). Further analysis by age (<4 years and ≥ 4 years) in the 3 studies showed no differences from the overall analyses in nighttime or daytime asthma symptom scores (data not shown). Nighttime and daytime asthma symptoms improved in all 3 studies; improvement was observed in the least severe asthma patients in study A to the most severe patients in study B.

Use of breakthrough medications

Mean changes in the number of days bronchodilator medications were required for treatment of breakthrough asthma symptoms during the 12-week double-blind period for each treatment group are shown in Fig 3 for studies A, B, and C. There were significant reductions in the

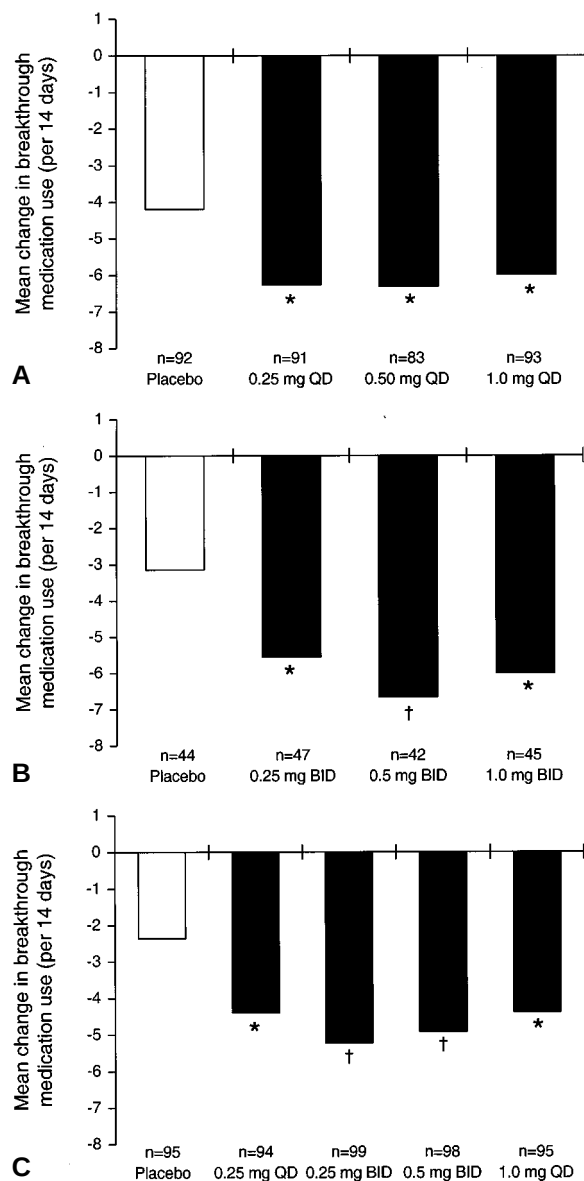


FIG 3. Mean change from baseline in the number of days bronchodilators were used per 14 days for breakthrough asthma symptoms. **A**, Patients whose asthma was not previously controlled with bronchodilators or noncorticosteroid anti-inflammatory agents. **B**, Patients whose asthma was previously treated with inhaled corticosteroids. (From Shapiro G, Mendelson L, Kraemer MJ, Cruz-Rivera M, Walton-Bowen K, Smith JA. Efficacy and safety of budesonide inhalation suspension [Pulmicort Respules] in young children with inhaled steroid-dependent, persistent asthma. *J Allergy Clin Immunol* 1998;102:789-96. By permission.) **C**, Patients whose asthma was previously treated with either bronchodilators or inhaled corticosteroids. * $P \leq .05$ and † $P \leq .01$ versus placebo.

number of days medications were required in each BIS treatment group compared with placebo ($P < .05$) in each of the 3 studies. In patients whose asthma was not previously treated with inhaled corticosteroids (study A), the average reductions in the number of days that rescue medication was used per 14 days were 6.3, 6.3, and 6.0 days for the 0.25-mg once daily, 0.5-mg once daily, and

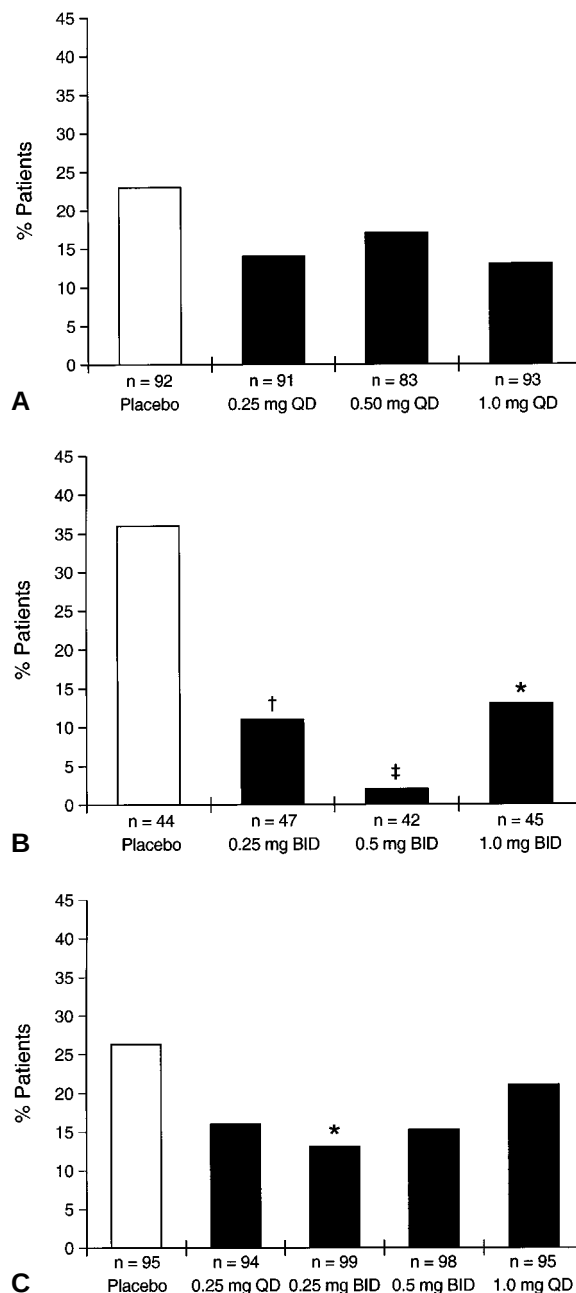


FIG 4. Treatment failures as the result of worsening asthma. **A**, Patients whose asthma was not previously controlled with bronchodilators or noncorticosteroid anti-inflammatory agents. **B**, Patients whose asthma was previously treated with inhaled corticosteroids. **C**, Patients whose asthma was previously treated with either bronchodilators or inhaled corticosteroids. * $P \leq .05$, † $P \leq .01$, ‡ $P \leq .001$ versus placebo.

1.0-mg once daily BIS treatment groups, respectively, as compared with 4.2 days in the placebo group ($P < .05$). In patients with more severe asthma who were dependent on inhaled corticosteroids (study B), the average reductions in the number of days that rescue medication was used per 14 days were 5.6, 6.7, and 6.0 days for the 0.25-mg twice daily, 0.5-mg twice daily, and 1.0-mg twice

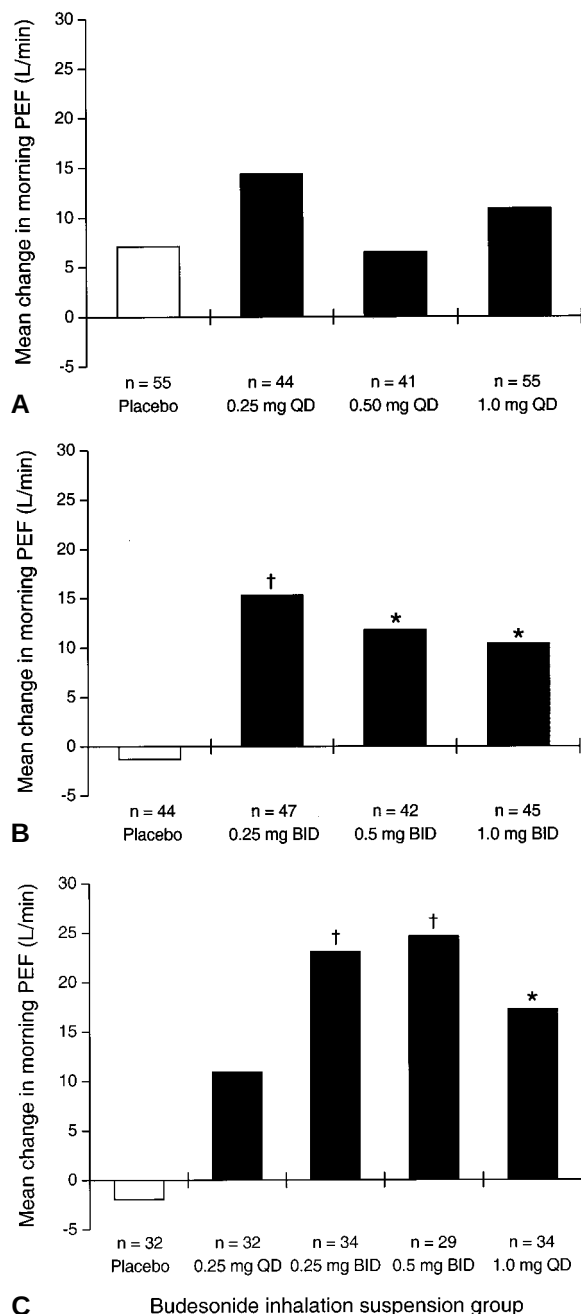


FIG 5. Mean change from baseline in morning PEF (L/min) over the 12-week, double-blind treatment period in patients capable of consistently performing pulmonary function tests. **A**, Patients whose asthma was not previously controlled with bronchodilators or noncorticosteroid anti-inflammatory agents. **B**, Patients whose asthma was previously treated with inhaled corticosteroids. **C**, Patients whose asthma was previously treated with either bronchodilators or inhaled corticosteroids. * $P \leq .05$, $^{\dagger}P \leq .01$ versus placebo.

daily BIS treatment groups, respectively, as compared with 3.1 days in the placebo group ($P \leq .032$). In study C, the average reductions in the number of days that rescue medication was used per 14 days were 4.4, 5.2, 4.9, and 4.4 days for the 0.25-mg once daily, 0.25-mg twice daily,

0.5-mg twice daily, and 1.0-mg once daily BIS treatment groups, respectively, as compared with 2.4 days in the placebo group ($P \leq .014$). These data show that BIS, administered once or twice daily, was effective in reducing the need for bronchodilators across studies despite differences in asthma severity.

Treatment failures because of worsening asthma

In each of the 3 studies, there were clear trends for patients with more severe asthma and patients in the placebo groups to discontinue treatment because of worsening of asthma symptoms at a higher rate than the BIS groups. Fig 4 shows patient discontinuation rates as the result of worsening asthma for studies A, B, and C. In patients with less severe asthma (study A), the proportion of patients who discontinued therapy because of worsening of asthma symptoms tended to be greater in the placebo group (23%) than in the BIS groups (14%, 17%, and 13% of patients in the 0.25-mg, 0.5-mg, and 1.0-mg once daily BIS groups, respectively).

In patients with more severe asthma that had previously been treated with inhaled corticosteroids before the study (study B), the proportion of patients who discontinued therapy because of worsening of asthma symptoms was significantly greater in the placebo group (36%) than in the BIS groups (9%; $P \leq .015$); 11%, 2%, and 13% of patients in the 0.25-mg, 0.5-mg, and 1.0-mg twice daily BIS groups, respectively, discontinued treatment because of worsening asthma.

In patients whose asthma was previously treated with either bronchodilators or inhaled corticosteroids (study C), the proportion of patients who discontinued therapy because of worsening of asthma symptoms was greater in the placebo group (26%) than in the BIS groups (16%, 13%, 15%, and 21% for the 0.25-mg once daily, 0.25-mg twice daily, 0.5-mg twice daily, and 1.0-mg once daily groups, respectively); the difference between 0.25-mg twice daily group and the placebo group was statistically significant ($P = .029$).

Morning and evening PEF levels

Mean changes in morning PEF levels in patients capable of consistently performing pulmonary function tests are shown in Fig 5 for studies A, B, and C. Treatment with BIS was associated with improvements in PEF levels. In the patients with less severe asthma in study A, all BIS doses except 0.5-mg once daily showed nonsignificant numeric improvements in morning (Fig 5, A) and evening PEF levels compared with placebo. Evening PEF levels increased from baseline by 3.6 L/min, 11.2 L/min, 3.8 L/min, and 9.9 L/min for the placebo, 0.25-mg once daily, 0.5-mg once daily, and 1.0-mg once daily BIS groups, respectively.

In study B (Fig 5, B), which included patients with more severe asthma, morning PEF levels were found to be significantly greater in each BIS group compared with placebo ($P \leq .03$). For evening PEF levels, all BIS treatment groups showed numeric improvement compared

with placebo, although the 0.25-mg twice daily BIS group showed statistically significant improvement ($P < .05$). Evening PEF levels increased from baseline by 3.0 L/min, 14.9 L/min, 11.6 L/min, and 13.2 L/min for the placebo, 0.25-mg twice daily, 0.5-mg twice daily, and 1.0-mg twice daily BIS groups, respectively. In study C (Fig 5, C), all BIS doses showed numeric improvement in morning PEF levels, and statistically significant improvements were observed in the 0.25-mg twice daily, 0.5-mg twice daily, and 1.0-mg once daily BIS treatment groups compared with placebo ($P < .03$). Significant improvements in evening PEF levels were observed for each BIS treatment group ($P \leq .034$), except for the 1.0-mg once daily group. Evening PEF levels increased from baseline by 1.9 L/min, 16.8 L/min, 19.2 L/min, 21.0 L/min, and 14.1 L/min for the placebo, 0.25-mg daily, 0.25-mg twice daily, 0.5-mg twice daily, and 1.0-mg once daily BIS groups, respectively.

FEV₁

Mean changes from baseline to the end of the 12-week treatment period for FEV₁ in each study are shown in Fig 6. In study A, mean changes in FEV₁ were -0.01 L, 0.03 L, and 0.03 L for the 0.25-mg once daily, 0.5-mg once daily, and 1.0-mg once daily BIS treatment groups, respectively, compared with -0.07 L for placebo. Statistically significant improvements in FEV₁ were observed in the 0.5-mg ($P = .044$) and 1.0-mg ($P = .033$) BIS groups compared with placebo. For patients with more severe asthma in study B (Fig 6, B), a statistically significant improvement in FEV₁ was observed in the 0.5-mg twice daily BIS group compared with placebo ($P = .043$). In patients whose asthma was previously treated with bronchodilators or inhaled corticosteroids (study C), all treatment groups showed numeric improvement in FEV₁; statistically significant improvement in FEV₁ compared with placebo was observed in the 0.5-mg twice daily BIS group ($P = .031$).

Other measures of pulmonary function, forced vital capacity and forced expiratory flow showed a trend toward improvement in the BIS-treatment groups compared with placebo (data not shown) in studies A and B.

DISCUSSION

Three double-blind, placebo-controlled, randomized clinical trials of 12-week duration have shown that, compared with placebo, BIS significantly decreases nighttime and daytime asthma symptoms and reduces β_2 -agonist use for breakthrough asthma symptoms, when given once daily or twice daily in doses of 0.25, 0.5, and 1.0 mg. Morning PEF levels were significantly improved in most dose groups, and evening PEF levels showed a clear trend toward improvement in all BIS groups compared with placebo. Improvements in nighttime and daytime asthma symptom scores (0-3 scale) were observed within 2 to 5 days after initiation of treatment. The reduction in nighttime and daytime asthma symptoms was maintained throughout the 12-week double-blind treatment periods.

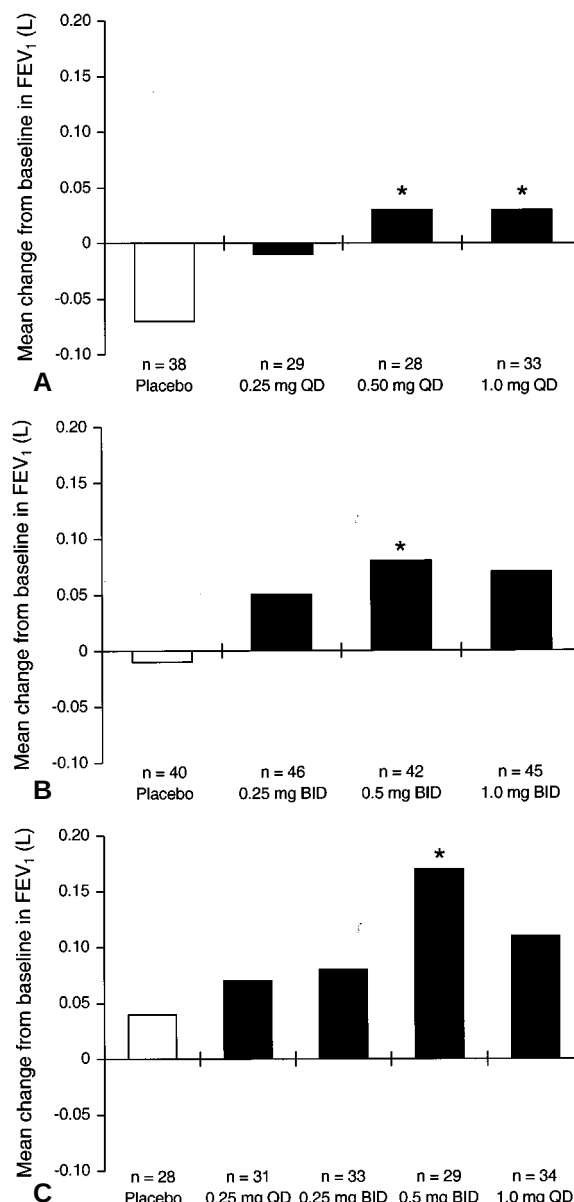


FIG 6. Mean change from baseline in FEV₁ level (liters) over the 12-week, double-blind treatment period in patients capable of performing consistent spirometry. **A**, Patients whose asthma was not previously controlled with bronchodilators or noncorticosteroid anti-inflammatory agents. (From Kemp JP, Skoner D, Szefer SJ, Walton-Bowen K, Cruz-Rivera M, Smith JA. Once-daily budesonide inhalation suspension for the treatment of persistent asthma in infants and young children. *Ann Allergy Asthma Immunol* 1999;83:231-9. By permission.) **B**, Patients whose asthma was previously treated with inhaled corticosteroids. **C**, Patients whose asthma was previously treated with either bronchodilators or inhaled corticosteroids. * $P \leq .05$ versus placebo.

BIS improved asthma symptoms and pulmonary function in 3 different patient populations: patients whose asthma was previously treated with bronchodilators or inhaled noncorticosteroid anti-inflammatory agents, patients whose asthma was previously treated with either

bronchodilators or inhaled corticosteroids, and patients whose asthma was previously treated with inhaled corticosteroids. The type of treatment is indicative of the severity of their asthma. National Asthma Education and Prevention Program asthma treatment guidelines recommend that mild intermittent asthma be controlled with bronchodilators as needed for symptoms that occur 2 times or less each week, that mild persistent asthma be treated with daily noncorticosteroid anti-inflammatory medications or low-dose inhaled corticosteroids with bronchodilators as needed for symptoms, that moderate persistent asthma be treated with medium-dose inhaled corticosteroids and noncorticosteroid anti-inflammatory medications with bronchodilators as needed for symptoms, and that severe persistent asthma be treated with high-dose inhaled corticosteroids and systemic corticosteroids (if needed) with bronchodilators as needed for symptoms.¹ All patients treated with corticosteroids should be titrated to the lowest effective dose that effectively controls asthma symptoms. The present studies were conducted in patients, with varying levels of asthma severity, whose asthma was inadequately controlled on study entry.

Although nighttime and daytime asthma symptom scores were consistently improved by all budesonide treatment regimens, spirometry results were more variable; FEV₁ measurements showed statistical improvement in some BIS groups, whereas other active treatment groups showed numeric improvement or no improvement. The inconsistencies in spirometry results may be due to a high degree of variability between individual subjects; because of their youth and inexperience, it is difficult to obtain uniform pulmonary function tests in children under 4 years of age.^{1,5,21-24} Nevertheless, the variability in spirometry measures most likely resulted in an underestimate, rather than an overestimate of budesonide's efficacy.

This article reviews the efficacy of a wide range of daily doses of BIS (0.25 mg to 2.0 mg) in patient populations with varying levels of asthma severity. Although a dose-related trend was observed with some of the efficacy variables across studies, overall, large differences in improvement were not observed between the different BIS treatment regimens. The lack of dose-response relationships in the 3 trials is not surprising because it appears that demonstration of a dose-related effect with inhaled corticosteroids may be dependent on several factors, including variation between individual patients in asthma severity, efficacy measure, and patient cooperation and inhalation technique. For example, 2 studies have shown that budesonide doses ranging from 0.5 to 4.0 mg daily were equally effective in children with mild-to-moderate asthma.^{16,26} In contrast, Grimfeld et al¹³ found 0.50-mg BIS daily to be less effective in protecting against acute asthma exacerbations than 2.0-mg BIS daily in children with moderate-to-severe asthma, but only as measured by the number of wheezing episodes and not by the need for systemic steroid therapy. In another study,²⁷ a significant dose-response rela-

tionship with budesonide suspension (0.5 mg, 1.0 mg, or 2.0 mg twice daily) was observed in measures of pulmonary function (FEV₁, PEF, and forced midexpiratory flow), but not in morning and evening asthma symptoms, in 6 to 15-year-old children with moderate asthma. Factors such as patient cooperation and inhalation technique may have been partly responsible for not demonstrating a dose response in the set of studies described here; it is difficult to obtain accurate pulmonary function and spirometry readings in young children. Furthermore, in all 3 studies, symptom scores were defined by the caregivers rather than the child, adding to variability in results. In children with mild-to-moderate asthma in study A, BIS 0.25 mg once daily produced a significant reduction in asthma symptoms, although in children with moderate-to-severe asthma in study B, BIS 0.25 mg twice daily significantly reduced asthma symptoms. Although these studies provide an approximate estimate of the lowest effective doses for mild-to-moderate and moderate-to-severe asthma, it is important to individualize treatment and titrate down to the lowest effective budesonide dose based on asthma severity and response to treatment.

Inhaled corticosteroids are the most potent and effective anti-inflammatory agents available for the treatment of patients with persistent asthma.¹ BIS given by nebulizer will be an important new therapeutic option for the administration of inhaled anti-inflammatory therapy to infants and children younger than 4 years. The results of randomized, placebo-controlled, double-blind studies have clearly demonstrated that nebulized budesonide is effective and can easily be delivered to infants and children who lack the coordination and understanding necessary to use pressurized metered-dose inhalers with a spacer or inhalation-driven devices. In addition, these data show that BIS, in a multiple-dose range, is effective in controlling asthma in infants and young children and that once-daily dosing is an option for the prescribing physician. Hence BIS will be the first nebulizable corticosteroid available for infants and young children younger than 4 years of age and will provide this patient population with an alternative for the treatment of persistent asthma.

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REFERENCES

1. National Asthma Education and Prevention Program. Expert panel report 2: guidelines for the diagnosis and management of asthma. Bethesda (MD): NIH/National Heart, Lung, and Blood Institute; 1997. Publication no. 97-4051.
2. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;88:373-81.
3. Haahela T, Järvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, et al. Effects of reducing or discontinuing budesonide in patients with mild asthma. *N Engl J Med* 1994;331:700-5.
4. Selroos O, Pietinalho A, Löfroos A-B, Riska H. Effect of early vs late intervention with inhaled corticosteroids in asthma. *Chest* 1995; 108:1228-34.
5. Foucard T. Aggressive treatment of childhood asthma with local steroids. Good or bad? *Allergy* 1996;51:367-71.
6. Lemanske RF Jr, Busse WW. Asthma. *JAMA* 1997;278:1855-73.
7. Powell CVE, Everard ML. Treatment of childhood asthma: options and rationale for inhaled therapy. *Drugs* 1998;55:237-52.
8. Bush A. Asthma in the child under five. *Br J Hosp Med* 1996;55:110-4.
9. Clough J. Asthma in the very young. *Practitioner* 1995;239:198-202.
10. Paton J. Managing asthma in the under twos. *Practitioner* 1996;240:576-84.
11. de Blic J, Delacourt C, Le Bourgeois M, Mahut B, Ostinelli J, Caswell C, et al. Efficacy of nebulized budesonide in treatment of severe infantile asthma: a double-blind study. *J Allergy Clin Immunol* 1996;98:14-20.
12. Godfrey S, Arital A, Rosler A, et al. Nebulized budesonide in severe infantile asthma. *Lancet* 1987;2:851-2.
13. Grimfeld A, Lesbros D, Ostinelli J, Caswell C. Long term study of nebulized budesonide in young children with moderate to severe asthma. [abstract]. *Eur Respir J* 1994;7(suppl):27S.
14. Hultquist C. Nebulized budesonide in severe childhood asthma [letter]. *Lancet* 1989;1:380.
15. Ilangovan P, Pedersen S, Godfrey J, Nikander K, Noviski N, Warner JO. Treatment of severe steroid-dependent preschool asthma with nebulized budesonide suspension. *Arch Dis Child* 1993;68:356-9.
16. Pedersen S, Ramsgaard-Hansen O, Nikander K. Budesonide suspension for nebulization in children with asthma [abstract]. *Eur Respir J* 1989;2(suppl):647S.
17. Wennergren G, Nordvall SL, Hedlin G, Möller C, Wille S, Asbrink-Nilsson E. Nebulized budesonide for the treatment of moderate to severe asthma in infants and toddlers. *Acta Paediatr* 1996;85:183-9.
18. Baker J, Mellon M, Wald J, Welch M, Cruz-Rivera M, Walton-Bowen K. A multiple-dosing, placebo-controlled study of budesonide nebulizing suspension given once or twice daily for treatment of persistent asthma in young children and infants. *Pediatrics* 1999;103:414-21.
19. Kemp JP, Skoner D, Szeffler SJ, Walton-Bowen K, Cruz-Rivera M, Smith JA. Once-daily budesonide inhalation suspension for the treatment of persistent asthma in infants and young children. *Ann Allergy Asthma Immunol* 1999;83:231-9.
20. Shapiro G, Mendelson L, Kraemer MJ, Cruz-Rivera M, Walton-Bowen K, Smith JA. Efficacy and safety of budesonide inhalation suspension (Pulmicort Respules) in young children with inhaled steroid-dependent, persistent asthma. *J Allergy Clin Immunol* 1998;102:789-96.
21. Martinati LC, Boner AL. Clinical diagnosis of wheezing in early childhood. *Allergy* 1995;50:701-10.
22. Mueller GA, Eigen H. Pediatric pulmonary function testing in asthma. *Pediatr Clin North Am* 1992;39:1243-58.
23. Sly PD, Robertson CF. A review of pulmonary function testing in children. *J Asthma* 1990;27:137-47.
24. Williams PV. Management of asthma. *Clin Symp* 1997;49:2-32.
25. Calpin C, Macarthur C, Stephens D, Feldman W, Parkin PC. Effectiveness of prophylactic inhaled steroids in childhood asthma: a systematic review of the literature. *J Allergy Clin Immunol* 1997;100:452-7.
26. Vikre-Jørgensen J, Agertoft L, Pedersen S. Dose titration of nebulized budesonide in young children. *Pediatr Pulmonol* 1997;23:270-7.
27. Pedersen S, Hansen OR. Dose-response relationships to nebulized budesonide in children with asthma [abstract]. *Am J Respir Crit Care Med* 1997;155(suppl):A268.