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New products

Series editors: Donald Y. M. Leung, MD, PhD, Harold S. Nelson, MD, Stanley J. Szeffler, MD, Philip S. Norman, MD, and Andrea Apter, MD, MSc

Budesonide inhalation suspension: A nebulized corticosteroid for persistent asthma

Stanley J. Szeffler, MD, and Howard Eigen, MD

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Budesonide inhalation suspension: A nebulized corticosteroid for persistent asthma

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Guidelines for managing asthma in pediatric patients published by the American Academy of Allergy, Asthma, and Immunology and the American Academy of Pediatrics recommend the use of inhaled corticosteroids for the management of persistent asthma in infants and young children. When these guidelines were published, pressurized metered-dose inhalers and dry-powder inhalers were the only delivery devices available for inhaled corticosteroids in the United States. These devices can be difficult for young children to use correctly. Furthermore, no inhaled corticosteroid was approved in the United States for the treatment of children younger than 4 years. Budesonide inhalation suspension (Pulmicort Respules; AstraZeneca LP, Wilmington, Del) was developed to meet the medication delivery needs of infants and young children with persistent asthma. Pulmicort Respules is the first inhaled corticosteroid approved for administration by means of a nebulizer and the only inhaled corticosteroid approved in the United States for infants as young as 12 months. Budesonide has been studied extensively worldwide. In the United States the tolerability and efficacy of budesonide inhalation suspension were confirmed in 3 placebo-controlled multicenter trials. These studies demonstrated that both once- and twice-daily dosing of budesonide inhalation suspension (0.25-1 mg) improved pulmonary function and ameliorated asthma symptoms in infants and young children with persistent asthma. Budesonide inhalation suspension was well tolerated, and the incidences of reported adverse events were similar among patients in the budesonide, placebo, and conventional asthma therapy groups. This article reviews the results of these studies, as well as the pharmacokinetics, pharmacodynamics, and clinical use of budesonide inhalation suspension. (*J Allergy Clin Immunol* 2002;109:730-42.)

Key words: Asthma, budesonide, budesonide inhalation suspension, efficacy, inhaled corticosteroid, pediatric, Pulmicort Respules, safety

CLINICAL NEED FOR A NEBULIZED CORTICOSTEROID Incidence of asthma in infants and young children

Pediatric asthma is a major global health problem with substantial and costly effects on the family, health care services, and society.^{1,2} Asthma affects 4% to 5% of American children, with rates of prevalence, severity, and death on the rise since 1980.^{3,4} Data from family health status questionnaires show that prevalence rates for asthma increased 75% from 1980 to 1994, with the largest increase occurring in children 4 years of age or younger.⁴ This age group also had the highest rate of hospitalization; mortality rates during this period were slightly increased in the 0- to 4-year age group and nearly doubled for children 5 to 14 years of age.⁵ In addition, asthma morbidity, as measured by school and work loss, has increased over the 10-year period from 1985 to 1994.² These data suggest that children are at increasing risk for morbidity and death caused by asthma and highlight the importance of early detection and asthma management for the pediatric population.

Current management guidelines

Asthma management guidelines provided by the National Asthma Education and Prevention Program and published by the National Heart, Lung, and Blood Institute of the National Institutes of Health have established a stepwise approach for the diagnosis and treatment of asthma.⁶ Medications used in the treatment of asthma are classified into 2 categories: long-term control medications and quick-relief medications. Disease severity is divided into 4 classifications: mild intermittent, mild persistent, moderate persistent, and severe persistent. Children with mild intermittent asthma may be treated with quick-relief medication alone, and daily treatment may not be required.⁶ For all severities of persistent disease, long-term use of daily controller medication is recom-

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Abbreviations used

ACTH: Adrenocorticotrophic hormone
CAMP: Childhood Asthma Management Research Program
CAT: Conventional asthma therapy
PEF: Peak expiratory flow

mended to achieve and help sustain control of asthma symptoms. Of the long-term control medications, inhaled corticosteroids are recognized as the most potent and effective anti-inflammatory medications.⁶ Inhaled corticosteroids have become the mainstay of treatment for persistent asthma because of their effectiveness in relieving symptoms, improving pulmonary function, and reducing requirements for rescue medication.⁶⁻⁹

Treatment challenges

Because of challenges in conducting clinical trials in children, many medications used to treat pediatric asthma have not been intensively studied in children and do not have the necessary safety and efficacy data required by the Food and Drug Administration for pediatric labeling. In addition to ethical issues, challenges include reliance on the indirect assessment of symptoms and adverse events from caregivers, the failure of the caregiver to detect nighttime symptoms, and the inability of young children to perform pulmonary function tests. For these reasons, treatment of young children with inhaled corticosteroids has been complicated by a lack of approved products and by technical difficulties in drug delivery.

Until the recent approval of budesonide inhalation suspension (Pulmicort Respules; AstraZeneca LP, Wilmington, Del), no inhaled corticosteroid was approved in the United States for treatment of children younger than 4 years. In addition, available delivery devices are not designed for the pediatric population. Children younger than 4 years of age may have trouble using dry-powder inhalers because of low or variable inspiratory flow rates, resulting in a poor or inconsistent clinical response.^{6,10-13} A pressurized metered-dose inhaler with a spacer is often prescribed for young children, but children younger than 4 years often lack the coordination and understanding to use such devices effectively.^{6,14-16} Consequently, there are no dosing guidelines for use of these devices in children less than 4 years of age. In addition, parents or other caregivers must understand how to use spacers, holding chambers, and face masks appropriately.⁶ Failure to shake the canister before each actuation and related practical difficulties in assisting an uncooperative child may lead to suboptimal medication delivery.¹⁷ Large spacer devices may require the assistance of more than one adult for medication administration.¹⁷ Comparative studies of inhaled corticosteroids and delivery devices also are lacking in this young patient population. An important method of drug delivery to infants and young children is nebulization.^{6,18} Nebulizer delivery of budesonide has been shown to be effective, and budesonide inhalation has been approved for prophylactic and maintenance

treatment of persistent asthma in children 12 months to 8 years of age.¹⁹

NEBULIZED BUDESONIDE

Clinical pharmacology

Glucocorticoid and lipophilic properties. Asthma is characterized by airway inflammation. Corticosteroids have inhibitory effects on multiple cell types (eg, mast cells, eosinophils, macrophages, and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, and cytokines) that are involved in allergic and nonallergic inflammation.²⁰ Many of the cellular effects of corticosteroids likely to be important in asthmatic inflammation are believed to involve increased transcription of anti-inflammatory genes (eg, genes encoding lipocortin 1, secretory leukocyte protease inhibitor, IL-10, and β_2 -adrenoceptors) and decreased transcription of inflammatory genes.²¹ Budesonide, a nonhalogenated corticosteroid, exhibits potent glucocorticoid activity and weak mineralocorticoid activity.²² In standard in vitro models budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor than does cortisol.²³

Administration of budesonide by means of inhalation enables local delivery to the bronchial tree.²² In animal in vivo and human in vitro models microsomal enzymes in lung tissue catalyze the formation of fatty esters of budesonide in a reversible reaction.^{24,25} It is hypothesized that these lipophilic esters are retained in the large airways for a prolonged period of time, serving as a local depot of regenerable active budesonide.^{24,26} Active budesonide gradually becomes available to the receptor through hydrolysis of these stored esters. In a study in which 24 subjects were simultaneously administered intranasal single doses of budesonide and fluticasone propionate, unesterified budesonide and budesonide esters (oleate and palmitate) and fluticasone, respectively, were detected in nasal tissue biopsy specimens 6 hours after drug administration.²⁷ Unesterified budesonide was detected in 67% of the biopsy specimens at 24 hours compared with 25% detection for fluticasone. Although not an examination of the large airways, this study demonstrates the formation of budesonide esters and the retention of budesonide in the human nasal mucosa in vivo.

Relative activity. The potency of budesonide is 1000 times that of cortisol when assessed by the ability to inhibit ear edema formation in the rat.²³ The topical activity of budesonide is greater than that of beclomethasone dipropionate, betamethasone valerate, flunisolide, hydrocortisone butyrate, and triamcinolone acetonide and near that of fluticasone propionate in adults when tested with the human skin vasoconstriction assay.^{22,23} The relevance of skin potency assays to clinical therapy has not been established. Budesonide has a high ratio of topical anti-inflammatory activity to systemic activity, resulting from potent local anti-inflammatory activity, extensive first-pass metabolism of orally absorbed drug, and low potency of budesonide metabolites.²³

TABLE I. Nebulized budesonide pharmacokinetics in asthmatic children 3 to 6 years of age^{23,41}

Parameter	Value
Total systemic bioavailability (lung and oral)	6%
Time to peak plasma concentration	10-30 min
Peak plasma concentration	2.6 nmol/L
AUC per milligram nominal dose	4.6 nmol/L × h/mg
Volume of distribution at steady state	3 L/kg
Total systemic clearance	0.5 L/min
Elimination half-life	2.3 h

AUC, Area under plasma concentration–time curve.

Effects on inflammatory cells and mediators. Studies of airway inflammation in adults, including study of bronchoalveolar lavage fluid, indicate that bronchial hyperresponsiveness is correlated with increased eosinophil and mast cell concentrations.^{28,29} Although persistent wheezing may involve more than high levels of eosinophils and mast cells,³⁰ the immunopathology of pediatric asthma appears to be similar or identical to that of adult asthma.³¹ In studies assessing inflammatory cells in adult patients with newly diagnosed asthma, significant increases in mast cells, eosinophils, lymphocytes, and macrophages were measured in biopsy specimens of bronchial airway epithelium.³²⁻³⁴ Inhaled budesonide treatment reduced the numbers of these inflammatory cells compared with pretreatment values³⁴ and placebo values.³⁵

Effects on airway hyperresponsiveness. Changes in airway hyperresponsiveness may be demonstrated readily by altered sensitivity to bronchoconstrictor stimuli, most commonly histamine or methacholine.^{36,37} Regular treatment with inhaled corticosteroids results in improved airway responsiveness in adult patients with corticosteroid-dependent and corticosteroid-independent asthma.³⁸ These changes are dose dependent and occur concomitantly with improvement in clinical asthma severity. The therapeutic effects of conventional doses of orally inhaled budesonide are largely explained by its direct local action on the respiratory tract²³ because systemic absorption is not a significant factor in the clinical efficacy of inhaled budesonide.³⁹

Budesonide attenuates both the acute and the delayed decrease in FEV₁ after inhaled allergen challenge administered either as a single dose or as short-term dosing in adults.²³ Results of the Childhood Asthma Management Research Program (CAMP) indicate that inhaled budesonide continues to reduce airway hyperresponsiveness in children with long-term treatment.⁴⁰ When inhaled budesonide was discontinued, airway hyperresponsiveness increased.

Pharmacokinetics

The pharmacokinetics of most inhaled corticosteroids has not been studied in young children. The pharmacokinetics of budesonide, however, has been assessed in healthy adults and asthmatic children and by means of

various administration routes. The pharmacokinetic properties of budesonide inhalation suspension in asthmatic children are summarized in Table I.^{23,41} No differences in pharmacokinetics on the basis of race, sex, or age have been identified.^{23,41}

Budesonide, a moderately lipophilic compound, is rapidly absorbed through lung mucosa and parenchyma.⁴² Peak plasma concentrations occur 10 to 30 minutes after the start of nebulization.²³ In asthmatic children 3 to 6 years of age, approximately 18% of the dose to the subject is deposited in the lung compared with 58% to 70% deposition in adults.⁴¹ In contrast, deposition in the oropharynx was higher in these children (approximately 82%) than in adults (30%-42%). The portion of medication deposited in the oropharynx is assumed to be swallowed. Thus in these asthmatic children systemic availability (pulmonary plus oral) is only approximately 6% of the labeled dose because of rapid, effective clearance from plasma by way of extensive first-pass metabolism of orally ingested drug.^{23,41} Total systemic bioavailability for other inhaled corticosteroid products has not been reported for children. For products available in the United States, studies in adults show that the absolute systemic bioavailability is 26% to 29% for the fluticasone propionate metered-dose inhaler, approximately 17% for the fluticasone propionate dry-powder formulation administered through the Diskus (GlaxoSmithKline, Research Triangle Park, NC),⁴³ and 62% for beclomethasone-17-monopropionate (active metabolite) after administration of beclomethasone dipropionate by means of a metered-dose inhaler.⁴⁴

The systemic clearance of nebulized budesonide in asthmatic children aged 3 to 6 years (0.5 L/min) is approximately 50% greater than that in healthy adults after adjustment for differences in body weight.^{23,41} The higher clearance per kilogram of body weight coupled with the low systemic availability in children enables use of the same nominal doses of budesonide administered through a nebulizer in children as in adults, despite their differences in body size.⁴¹ Exposure to budesonide, defined as area under the plasma concentration–time curve per milligram of nominal dose, is similar in children and adults.²³ The terminal half-life of budesonide after nebulization is 2.3 hours. In comparison, a pharmacokinetic study of fluticasone, 110 µg, administered through a metered-dose inhaler to 5 children (mean age, 6.6 years; range, 5-9 years) demonstrated that fluticasone clearance also was nearly twice as high in children as in adults.⁴⁵ Compared with adults who received a similar inhaled dose, fluticasone plasma concentrations were lower in children. The authors postulated that these differences resulted from either less efficient drug delivery to the children's airways, more rapid metabolism, or both. The mean estimated half-life of 5.7 hours (range, 4.7-7.5 hours) in these asthmatic children was similar to the reported half-life of 6 hours in adults. Pharmacokinetic data for children less than 3 years of age are not available for any inhaled corticosteroid product. It is anticipated that systemic clearance in younger children would be

TABLE II. Designs for 3 US studies of budesonide inhalation suspension

Reference	Age	Asthma diagnosis	Prior ICS use	Treatment groups
Kemp et al, 1999 ⁵⁸	6 mo-8 y	Mild persistent	No	Placebo, 0.25 mg qd, 0.5 mg qd, 1 mg qd
Shapiro et al, 1998 ⁵⁹	4-8 y	Moderate persistent; PFTs required	Yes	Placebo, 0.25 mg bid, 0.5 mg bid, 1 mg bid
Baker et al, 1999 ⁵⁷	6 mo-8 y	Moderate persistent	Optional	Placebo, 0.25 mg qd, 0.25 mg bid, 0.5 mg bid, 1 mg qd

ICS, Inhaled corticosteroid; qd, once daily; bid, twice daily; PFT, pulmonary function test.

slower and more variable within the population because of varying developmental maturation of the metabolic pathways. Further studies are needed in this age group.

Budesonide is extensively bound to plasma proteins (85%-90%).²³ Protein binding is constant over the concentration range of 1 to 100 nmol/L, which includes the concentrations achieved with recommended doses of budesonide. In asthmatic children 3 to 6 years of age, the mean volume of distribution of budesonide at steady state is 3 L/kg.⁴¹ In comparison, the mean volume of distribution of budesonide in healthy adults is 2.69 L/kg.⁴⁶

Budesonide is cleared primarily in the liver, with rapid, extensive metabolism and excretion of metabolites in urine and feces.^{41,47} Cytochrome P450 3A catalyzes its biotransformation into 2 major metabolites, 16 α -hydroxyprednisolone and 6 β -hydroxybudesonide. The receptor-binding potencies and anti-inflammatory activities of these metabolites are greatly reduced ($\leq 1\%$) compared with those of budesonide.⁴⁸⁻⁵⁰

Clinical efficacy

Nebulized budesonide has been studied extensively in more than 34 countries.⁵¹⁻⁵⁶ Studies conducted outside of the United States demonstrated the efficacy and safety of nebulized budesonide (0.25-1 mg administered twice daily) in infants and young children 5 months to 5 years of age with moderate-to-severe asthma.⁵¹⁻⁵⁵ Compared with placebo, nebulized budesonide significantly reduced symptoms, including daytime and nighttime wheeze, asthma exacerbations, and oral prednisone use.^{51,53-55} Nebulized budesonide (0.5-2 mg administered twice daily) improved pulmonary function, subjective symptom scores, and β_2 -agonist use in children older than 6 years of age with mild-to-moderately severe asthma.⁵⁶ Improvements in FEV₁ were dose related.

This review will focus on 3 large, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies conducted in the United States to assess the efficacy and safety of nebulized budesonide in children 6 months to 8 years of age.⁵⁷⁻⁵⁹ A total of 1018 pediatric patients with persistent asthma of varying duration (range, 2-107 months) and severity were included in the studies.⁵⁷⁻⁵⁹ Three populations were studied: patients not receiving inhaled corticosteroids,⁵⁸ patients previously maintained on inhaled corticosteroids,⁵⁹ and a combined population of patients with asthma that was previously controlled with either bronchodilators or corticosteroids⁵⁷ (Table II). No oral corticosteroids were permitted within 30 days of initiation of each study. Budesonide doses of 0.25 mg, 0.5 mg, and 1 mg administered either once or twice daily were delivered by means of a PARI LC PLUS jet nebulizer with a face mask or mouthpiece connected to a PARI Master compressor (PARI Respiratory Equipment, Inc, Midlothian, Va).

Each of the 3 studies had a similar design, consisting of a 2-week baseline period, followed by a 12-week double-blind treatment period, with evaluations every 2 to 4 weeks.⁵⁷⁻⁵⁹ Primary efficacy variables were mean changes from baseline in nighttime and daytime asthma symptom scores over the 12-week study period. Secondary efficacy variables included study discontinuations and as-needed bronchodilator use for breakthrough asthma symptoms. Spirometry results, including FEV₁, forced expiratory flow at 25% to 75% of vital capacity, forced vital capacity, and morning and evening peak expiratory flow (PEF), were evaluated in patients capable of consistently performing these tests. Symptoms were recorded daily on diary cards by caregivers using a 4-point scale (0 = none to 3 = severe) and were reviewed at each clinic visit. Evaluations conducted at the beginning and end of the study period included a comprehensive physical examination, clinical laboratory assessments, and documentation of reversibility of airway obstruction.

Efficacy analyses included all patients who received at least 1 dose of study medication and had at least 1 observation taken while receiving study medication.⁵⁵⁻⁵⁷ Data for patients who terminated the study early or had missing data were included in the analyses. ANOVA was used to compare each active nebulized budesonide treatment group with the placebo group for all efficacy variables, with the exception of patient outcomes, which were assessed with the Fisher exact test.

Efficacy of once-daily nebulized budesonide in non-corticosteroid-dependent children. Children 6 months to 8 years of age (N = 359) with stable asthma who were using at least one long-term asthma medication daily and a bronchodilator periodically for at least 3 months were enrolled.⁵⁸ An FEV₁ of 50% or greater of predicted normal value, with reversibility of 15% or greater after a standard dose of albuterol, was required in patients who could perform pulmonary function tests. Patients were randomized to receive once-daily placebo (n = 92) or nebulized budesonide, 0.25 mg (n = 91), 0.5 mg (n = 83), or 1 mg (n = 93). Demographics and baseline asthma characteristics were similar between the combined budesonide groups and the placebo group (Tables III and IV).⁵⁷⁻⁵⁹

TABLE III. Baseline demographics

Characteristic	Kemp et al, 1999 ⁵⁸ (N = 359)		Shapiro et al, 1998 ⁵⁹ (N = 178)		Baker et al, 1999 ⁵⁷ (N = 481)	
	BIS (n = 267)	Placebo (n = 92)	BIS (n = 134)	Placebo (n = 44)	BIS (n = 386)	Placebo (n = 95)
Mean age (y)	4.6	5.0	6.7	6.7	4.5	4.8
Sex, M/F (%)	66/44	65/35	67/33	46/54	65/35	62/38
Race (%)						
White	72	76	84	84	79	86
Black	16	13	9	14	15	7
Hispanic	8	10	5	2	4	4
Other	4	1	2	0	2	3

BIS, Budesonide inhalation suspension.

TABLE IV. Baseline asthma characteristics

Characteristic	Kemp et al, 1999 ⁵⁸ (N = 359)		Shapiro et al, 1998 ⁵⁹ (N = 178)		Baker et al, 1999 ⁵⁷ (N = 481)	
	BIS (n = 267)	Placebo (n = 92)	BIS (n = 134)	Placebo (n = 44)	BIS (n = 386)	Placebo (n = 95)
Mean duration of asthma (y)	3.0	3.1	4.3	4.2	2.8	3.0
Mean nighttime asthma symptom score	1.23	1.08	1.07	1.18	1.23	1.16
Mean daytime asthma symptom score	1.36	1.27	1.34	1.33	1.28	1.27
Able to perform PFT (%)	34	42	100	100	34	34
Mean PEF (L/min)						
Morning	136.4	143.9	161.7	158.3	160.9	155.8
Evening	145.0	150.7	167.3	164.7	170.1	160.8
FEV ₁ (% predicted)	81.2	81.6	79.9	79.2	80.0	79.1

BIS, Budesonide inhalation suspension; PFT, pulmonary function test.

All nebulized budesonide treatment groups showed significant improvements in nighttime and daytime asthma symptom scores compared with those seen in the placebo group ($P \leq .05$, Fig 1).⁵⁸ Improvement in asthma symptoms was observed in 2 to 8 days and was maintained throughout the 12-week study period. Significant reductions also were measured in breakthrough bronchodilator use per 2-week interval ($P \leq .05$, Fig 2). The average reductions in number of days that rescue medication was used per 2-week period ranged from 6.0 to 6.3 days in the budesonide groups compared with 4.2 days in the placebo group. Therapy discontinuations caused by worsening asthma occurred in a greater proportion of patients receiving placebo (23%) than in patients who received nebulized budesonide (13%-17%). In children able to demonstrate consistent spirometry testing (36% could execute a measurable FEV₁; >50% could perform PEF), those given budesonide showed improvements for mean changes in morning PEF, FEV₁, forced vital capacity, and forced expiratory flow at 25% to 75% of vital capacity compared with changes in the placebo group. FEV₁ significantly improved after budesonide doses of 0.5 and 1 mg (0.03 L in both groups) compared with that seen in the placebo group (-0.07 L, $P \leq$

.05). This study demonstrates that once-daily nebulized budesonide is an effective treatment for infants and young children (6 months to 8 years of age) with mild or moderate persistent asthma that is not adequately controlled with a bronchodilator or other noncorticosteroid asthma medication.

Efficacy of twice-daily nebulized budesonide in corticosteroid-dependent children. Children 4 to 8 years of age with stable persistent asthma who were corticosteroid dependent were randomized to receive placebo ($n = 44$) or nebulized budesonide, 0.25 mg ($n = 47$), 0.5 mg ($n = 42$), or 1 mg ($n = 45$), twice daily.⁵⁹ Patients who had an FEV₁ of 50% or greater of predicted normal value with reversibility of 15% or greater after albuterol were using daily inhaled corticosteroids and a bronchodilator for breakthrough symptoms for at least 3 months. Demographic and baseline asthma characteristics, including pulmonary function, were similar across groups (Tables III and IV).

Over the course of the study, patients given nebulized budesonide demonstrated significant improvements in nighttime and daytime asthma symptom scores compared with those in the placebo group ($P \leq .05$, Fig 3).⁵⁹ Improvements were observed 2 weeks after beginning treatment and were maintained through the end of the 12-

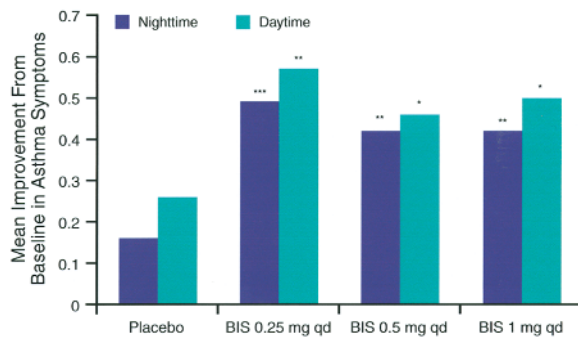


FIG 1. Mean improvement from baseline in nighttime and daytime asthma symptoms over the 12-week study period. * $P \leq .05$, ** $P \leq .01$, and *** $P \leq .001$ versus placebo. Mean change adjusted for center effect. BIS, Budesonide inhalation suspension; qd, once daily. Adapted with permission from *Ann Allergy Asthma Immunol*. 1999;83:231-9.

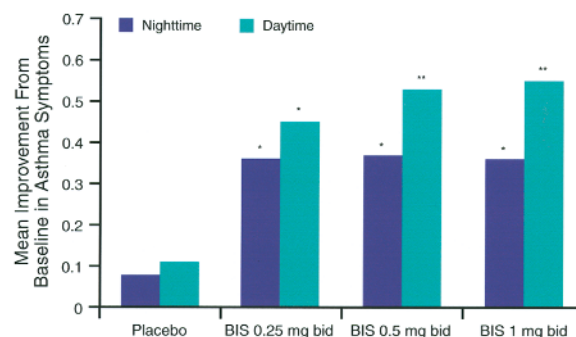


FIG 3. Mean improvement from baseline in nighttime and daytime asthma symptoms over the 12-week study period. * $P \leq .05$ and ** $P \leq .01$ versus placebo. Mean change adjusted for center effect. BIS, Budesonide inhalation suspension; qd, once daily. Adapted with permission from *J Allergy Clin Immunol*. 1998;102:789-96.

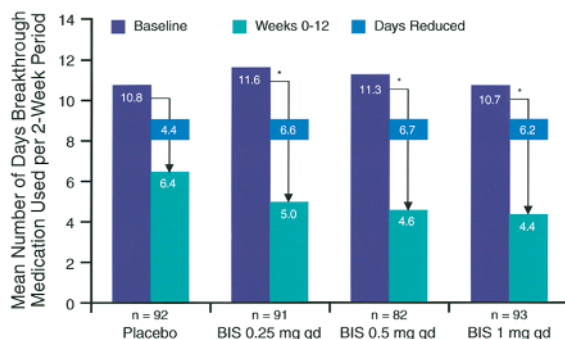


FIG 2. Mean number of days of breakthrough medication used per 2-week period at baseline and at the end of the 12-week study period. * $P \leq .05$ versus placebo. BIS, Budesonide inhalation suspension; qd, once daily. Data from *Ann Allergy Asthma Immunol*. 1999;83:231-9.

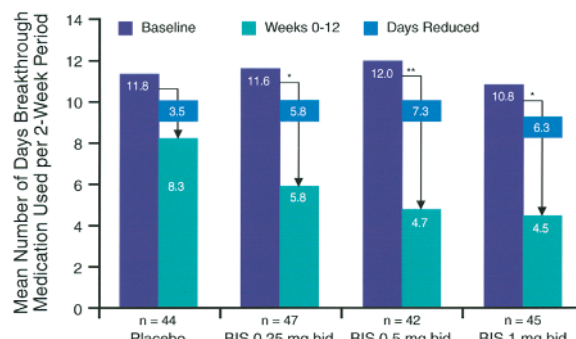


FIG 4. Mean number of days of breakthrough medication used per 2-week period at baseline and at the end of the 12-week study period. * $P \leq .05$ and ** $P \leq .01$ versus placebo. BIS, Budesonide inhalation suspension; bid, twice daily. Adapted with permission from *J Allergy Clin Immunol*. 1998;102:789-96.

week treatment period. Breakthrough medication use also was significantly reduced in patients receiving nebulized budesonide compared with that seen in the placebo group ($P \leq .05$, Fig 4). In addition, a smaller proportion of patients given nebulized budesonide (5%-18%) required a course of systemic corticosteroids compared with patients receiving placebo (36%). More patients given placebo discontinued the study because of worsening asthma (36%) than those given nebulized budesonide (2%-13%, $P \leq .02$).

Children in the active treatment groups also achieved significant improvement in pulmonary function compared with those in the placebo group. The mean change in morning PEF was significantly greater in the nebulized budesonide groups versus that in the placebo group ($P \leq .05$, Fig 5).⁵⁹ In addition, patients receiving nebulized budesonide, 0.5 mg twice daily, also demonstrated a significant improvement in FEV₁ (0.08 L) compared with that seen in the placebo group (-0.01 L, $P < .05$). This study shows that corticosteroid-dependent, persistent asthma in young children may be treated effectively with a twice-daily regimen of nebulized budesonide.

Efficacy of once- or twice-daily nebulized budesonide. In this study children 6 months to 8 years of age with moderate persistent asthma were randomized to treatment with placebo ($n = 95$) or nebulized budesonide, 0.25 mg once daily ($n = 94$), 0.25 mg twice daily ($n = 99$), 0.5 mg twice daily ($n = 98$), or 1 mg once daily ($n = 95$).⁵⁷ At study entry, all patients were using at least one asthma medication daily (excluding long-term systemic corticosteroids) plus a periodic bronchodilator for breakthrough symptoms. Thirty-one percent were previously treated with a stable dose of an inhaled corticosteroid for at least 2 months before enrollment, and similar proportions of these inhaled corticosteroid-dependent patients were included within each randomized treatment group (25%-34% in the budesonide groups; 38% in the placebo group). In patients able to perform pulmonary function tests consistently, a baseline FEV₁ of 50% or greater of predicted value was required, with 15% or greater reversibility after albuterol. Age, duration of asthma, and baseline symptom scores in patients who received budesonide were comparable with those of the patients who received placebo (Tables III and IV).⁵⁷

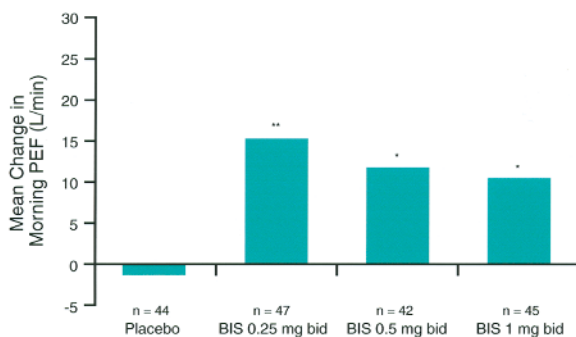


FIG 5. Mean change from baseline in morning PEF. * $P \leq .05$ and ** $P \leq .01$ versus placebo. Mean change adjusted for center effect. BIS, Budesonide inhalation suspension; bid, twice daily. Data from *J Allergy Clin Immunol*. 1998;102:789-96.

Image available in print only

FIG 6. Mean improvement from baseline in nighttime and daytime asthma symptoms over the 12-week study period. * $P \leq .05$, ** $P \leq .01$, and *** $P \leq .001$ versus placebo. Mean change adjusted for center effect. BIS, Budesonide inhalation suspension; qd, once daily; bid, twice daily. Adapted with permission from *Pediatrics*. 1999;103:414-21.

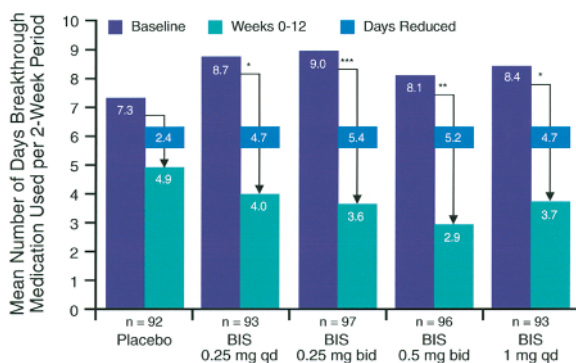


FIG 7. Mean number of days of breakthrough medication used per 2-week period at baseline and at the end of the 12-week study period. * $P \leq .05$, ** $P \leq .01$, and *** $P \leq .001$ versus placebo. BIS, Budesonide inhalation suspension; qd, once daily; bid, twice daily. Data from *Pediatrics*. 1999;103:414-21.

All nebulized budesonide groups demonstrated greater improvement in nighttime asthma symptom scores compared with that seen in the placebo group over the 12-week treatment period (Fig 6), and differences were significant in the groups that received nebulized budesonide,

0.25 mg twice daily, 0.5 mg twice daily, and 1 mg once daily ($P \leq .01$).⁵⁷ Similar results were reported for daytime symptom scores. When analysis was performed on data combined from all active treatment groups, a significant difference compared with that seen with placebo was observed as early as day 2 for nighttime symptoms and day 5 for daytime symptoms ($P \leq .05$). Days of breakthrough symptoms requiring bronchodilator use were significantly reduced in active treatment groups compared with the placebo group ($P < .01$, Fig 7). Of the one third of patients who could consistently perform pulmonary function tests, morning PEF results were significantly improved with nebulized budesonide, 0.25 mg twice daily, 0.5 mg twice daily, and 1 mg once daily, compared with placebo ($P < .03$, Fig 8). Improvements of 17 to 21 L/min also were observed in evening PEF in some treatment groups (nebulized budesonide, 0.25 mg once daily and 0.25 mg and 0.5 mg twice daily; $P < .05$). Patients in all nebulized budesonide dose groups demonstrated improvements in FEV₁, and differences were significant in the group that received nebulized budesonide, 0.5 mg twice daily ($P < .05$). Overall, data from this group of young children with moderate persistent asthma confirm the efficacy of once- or twice-daily nebulized budesonide, as reported in the 2 previous studies.

Efficacy by patient age. In a retrospective analysis of pooled data from 2 of the US studies described above,^{57,58} the efficacy of nebulized budesonide administered either once or twice daily was compared in patients less than 4 years of age and in those 4 years of age or older.^{60,61} Patients in both age groups demonstrated significant improvement in nighttime and daytime asthma symptom scores with nebulized budesonide treatment compared with that seen with placebo ($P \leq .05$), and requirements for breakthrough medication were reduced with active treatment. The results of the age-stratification analysis were consistent with those observed in the original studies for once- and twice-daily administration of nebulized budesonide. Importantly, demonstration of efficacy in children less than 4 years of age supports the findings of previous European studies of nebulized budesonide in children less than 4 years of age (5-60 months).^{51,53-55}

Efficacy of budesonide administered by means of nebulizer with face mask or mouthpiece. Nebulizers may be used with a face mask or a mouthpiece, the choice of which is typically dependent on patient age and level of cooperation. Studies comparing the use of face masks or mouthpieces for aerosol treatments have reported similar results for both devices.⁶² In 2 of the 3 studies of nebulized budesonide,^{57,58} a retrospective analysis was conducted to compare administration by means of a face mask with that by means of a mouthpiece.^{63,64}

In both analyses, alleviation of symptoms and reduction in breakthrough medication use were achieved with either a face mask or a mouthpiece.^{63,64} Improvements in efficacy variables for both administration devices were measured. Differences between treatment groups using face masks and mouthpieces compared with those of the

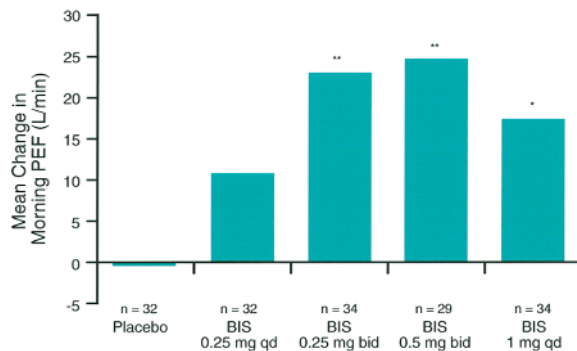


FIG 8. Mean change from baseline in morning PEF. * $P \leq .05$ and ** $P \leq .01$ versus placebo. Mean change adjusted for center effect. BIS, Budesonide inhalation suspension; qd, once daily; bid, twice daily. Data from *Pediatrics*. 1999;103:414-21.

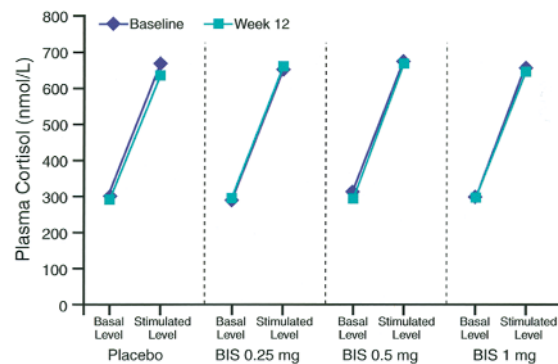


FIG 9. Basal and ACTH-stimulated cortisol levels at baseline and at week 12 from the double-blind studies. Basal level represents morning plasma cortisol. The 30- to 60-minute short ACTH-stimulation test was used. BIS, Budesonide inhalation suspension. Adapted with permission *J Allergy Clin Immunol*. 1999;104:S200-9.

placebo group using face masks ($n = 33$) or mouthpieces ($n = 59$) did not reach statistical significance, most likely because of small sample sizes.

Efficacy considerations. Supporting the results of studies conducted outside of the United States,^{51,53-55} the results of the 3 double-blind studies conducted in the United States demonstrate that budesonide inhalation suspension is effective when compared with placebo.⁵⁷⁻⁵⁹ Asthma symptoms and pulmonary function would be expected to worsen in the placebo groups because these patients, previously maintained on controller medications, were not allowed controller treatment in any of the studies. Improvements noted in the placebo group may have resulted from seasonal asthma or viral-induced asthma that improved over time. Participation in a clinical trial also may have benefited children in the placebo group because of improved patient education and early intervention with breakthrough medication. In the study of inhaled corticosteroid-dependent children, patients receiving placebo who were not discontinued from the study were able to control their symptoms by using rescue medications, which were used more frequently by patients in the placebo group compared with those in the budesonide group.⁵⁹ In all 3 trials more patients discontinued from the placebo groups for worsening asthma symptoms compared with those in the budesonide groups. Their symptom and pulmonary function data before discontinuation were carried forward, however, and included in the efficacy analysis. If these patients receiving placebo had remained in the studies, worsening symptom scores and pulmonary function would be expected.

A dose-response trend was observed with some efficacy variables in only one of the original 3 studies⁵⁷ and not at all after patients were stratified by age.^{60,61} Dose-response trends are extremely difficult to demonstrate with inhaled corticosteroids. The difficulty in demonstrating a dose-response trend across the 3 pivotal trials may have been compounded by inclusion of children with mild-to-moderate asthma, who would be expected

to respond well to even minimal doses of nebulized budesonide. Furthermore, asthma is a highly variable disease,⁶ and these children also may have experienced a period of disease quiescence. Variability in results caused by differences in patient cooperation and inhalation technique, efficacy measures, and factors unique to studies conducted in children, such as caregiver assessment of symptoms and accuracy of pulmonary function tests, also may have contributed to the difficulty in demonstrating a dose-response relationship.

The 3 US studies provide evidence of efficacy in relation to symptoms and pulmonary function improvement with budesonide inhalation suspension. These outcome measures, which historically have been used in older children, could be replaced by age-specific measures for young children. For example, symptom-free days, reductions in acute exacerbations, and other measures of pulmonary function may be more relevant and sensitive indicators of treatment intervention. Other variables important to the patient/caregiver (eg, administration time, convenience, and cost) would be of value in determining optimal care for pediatric patients with asthma. Determination of the smallest change in a score that patients or caregivers consider important also would be of value.⁶⁵ Longer term studies similar to that of the CAMP, which demonstrated the efficacy of budesonide inhalation powder in improving airway responsiveness and asthma symptoms, are required to assess the potential for altering the course of the disease.⁴⁰

Budesonide administered by means of a pressurized metered-dose inhaler or a Turbuhaler (AstraZeneca, Lund, Sweden) is used worldwide and has proved effective in asthma. Large multicenter trials comparing nebulized budesonide with budesonide or other inhaled corticosteroids delivered by means of a pressurized metered-dose inhaler with a spacer or a dry-powder inhaler have not been conducted in children. Furthermore, although less expensive delivery systems have been proved to be effective in older children, budesonide

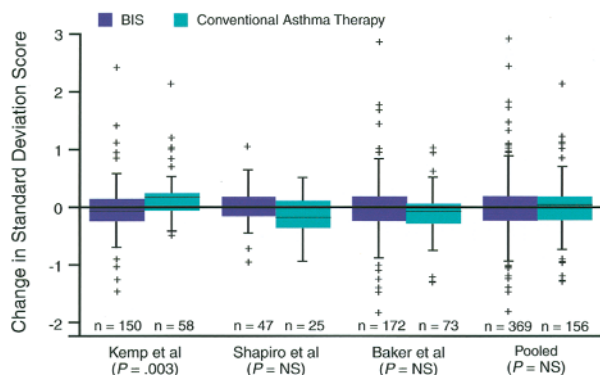


FIG 10. Growth velocity estimated from mean changes in height SD scores from baseline to week 52 by treatment group and study. The boxes span the 25th and 75th percentiles of the data, with the median noted by the inside bar. The length of the whiskers is based on 1.5 times the interquartile range, with outlying data points plotted individually. BIS, Budesonide inhalation suspension; NS, not significant. Reprinted with permission from *J Allergy Clin Immunol*. 1999;104:S200-9.

TABLE V. Adverse events with 10% or greater incidence reported in 52-week open-label studies⁶⁶

	CAT, n (%)	BIS, n (%)
Respiratory infection	109 (49)	259 (58)
Sinusitis	60 (27)	147 (33)
Fever	45 (20)	124 (28)
Otitis media	42 (19)	97 (22)
Pharyngitis	38 (17)	87 (19)
Accident, injury, or both	28 (13)	72 (16)
Rhinitis	24 (11)	76 (17)
Ear infection	24 (11)	58 (13)
Headache	23 (10)	51 (11)
Viral infection	27 (12)	41 (9)
Bronchitis	17 (8)	50 (11)
Gastroenteritis	16 (7)	44 (10)

CAT, Conventional asthma therapy; BIS, budesonide inhalation suspension.

TABLE VI. Dosage recommendations for budesonide inhalation suspension¹⁹

Previous therapy	Recommended starting dose	Highest recommended total daily dose
Bronchodilators alone	0.5 mg qd or 0.25 mg bid	0.5 mg
Inhaled corticosteroids	0.5 mg qd or 0.25 mg bid	1 mg
Oral corticosteroids	1 mg qd or 0.5 mg bid	1 mg

qd, Once daily; bid, twice daily.

inhalation suspension is the only inhaled corticosteroid treatment approved in the United States for children younger than 4 years. Currently, detailed studies in young children are limited by clear definitions of inclusion and exclusion criteria, difficulties in obtaining objective measures, and ethical concerns for treatment

selection and use of placebo. All of these areas are being addressed by the recognition that studies are urgently needed in young children with early-onset asthma, that asthma occurs early in childhood, and that the potential for irrecoverable loss may be the greatest within the early years of disease onset.

Safety

12-Week double-blind studies. Safety data collected during the 12-week double-blind phase of the 3 US nebulized budesonide pediatric studies included reports of adverse events, vital signs, physical examination results, and laboratory data.⁵⁶⁻⁵⁹ Pooled data from all 3 studies demonstrated that the incidence and nature of adverse events (not related to asthma) were similar in patients receiving placebo ($n = 231$) and those receiving nebulized budesonide ($n = 786$).⁶⁶ No dose-related adverse effects were apparent among the patients treated with budesonide. Commonly reported adverse events, regardless of the investigators' assessment of relationship to treatment, included respiratory infection, fever, sinusitis, otitis media, and rhinitis. Between the budesonide and placebo groups, the incidence of serious adverse events (2% vs 3%) and the proportion of patients who stopped treatment because of adverse events (1% vs 2%) were similar.⁶⁶

Hypothalamic-pituitary-adrenal axis function was assessed by obtaining measurements of both basal and adrenocorticotropic hormone (ACTH)-stimulated plasma cortisol concentrations. Plasma cortisol concentrations were determined both before and 60 minutes after administration of ACTH (0.25 mg administered intravenously in children aged >2 years and 0.125 mg administered intramuscularly in children aged ≤ 2 years). During the 12-week treatment periods in all 3 studies, similar basal and ACTH-stimulated cortisol concentrations were measured in a subset of patients from each study (Fig 9), with no significant differences between the placebo and budesonide groups.⁶⁶

Long-term (52-week) trials. After completion of the 12-week double-blind phase of each of the 3 US studies, a total of 670 patients were rerandomized in a 2:1 ratio to receive nebulized budesonide or conventional asthma therapy (CAT) for 52 weeks in an open-label trial.⁶⁶ Nebulized budesonide was initiated at a dose of 0.5 mg either once or twice daily; reduction to the lowest clinically effective dose was attempted at each subsequent study visit. CAT could include β_2 -agonists (short-acting oral and inhaled), methylxanthines, cromolyn sodium, or, in 2 of the studies, inhaled corticosteroids. The primary objective of these studies was to evaluate the overall safety of budesonide inhalation suspension in a typical clinical usage setting over 1 year.

The incidence and severity of adverse events, clinical laboratory values, oropharyngeal or nasal fungal cultures, and results of physical examinations were assessed. Although these studies were not designed specifically to assess the effects of budesonide on growth, parameters of height, growth velocity, and skeletal age were also evaluated at end point.⁶⁶ Height was

measured by means of stadiometry every 4 weeks and was normalized by comparing differences between observed height and standard median heights (50th percentile) on the basis of age and sex by using data from the National Center for Health and Statistics. Two of the studies also assessed skeletal age by using radiographs of the left hand–wrist obtained at weeks 0 and 52.⁶⁷

The incidence of reported adverse events over 52 weeks was similar between the 447 budesonide-treated and 223 CAT-treated patients in a pooled analysis of the 3 extension studies.⁶⁶ The most commonly reported adverse events were similar to those reported most frequently during the 12-week double-blind studies (Table V).⁶⁶ The proportions of patients who experienced serious adverse events or who discontinued treatment because of adverse events were similar in the budesonide and CAT groups. Vital signs, physical examination results, and laboratory test results (including nasal or oral fungal cultures) did not suggest any clinically significant differences between the nebulized budesonide and CAT study groups.⁶⁶ There were no reports of subcapsular or lenticular cataracts in these studies. Eye itching or irritation and skin-related local adverse effects were reported in 2% or less of patients receiving budesonide.⁶⁸ As in the double-blind study phase, the nebulized budesonide and CAT groups did not differ significantly in changes from baseline to week 52 in basal and ACTH-stimulated cortisol concentrations.

Of the 670 children randomized into the 52-week extension studies, a total of 371 subjects in the budesonide group and 156 subjects in the CAT group were included in the analysis of growth.⁶⁷ The pooled analysis of the 3 open-label studies showed no significant difference in growth between the budesonide and CAT groups over 52 weeks in all subjects or when stratified by sex or age. The distribution of changes in growth SD scores for the budesonide and CAT groups for each of the 3 open-label studies and for the pooled analysis is shown in Fig 10.

In one of the studies, a small but statistically significant difference in growth velocity (-0.8 cm/year) and height SD score was observed between the budesonide and CAT groups ($P \leq .005$).⁵⁸ These differences may have resulted from the increased number of outliers and the higher rate of discontinuations for worsening asthma in the CAT group compared with in the nebulized budesonide group. Alternatively, the difference may be explained by the fact that CAT-treated subjects in this study did not receive inhaled glucocorticosteroids, in contrast to those in the other 2 studies.⁶⁰ In those 2 studies, which assessed skeletal age, the mean differences between skeletal and chronologic ages for all children and for those stratified by sex were similar between the nebulized budesonide and CAT groups.

One of the challenges in assessment of growth during inhaled corticosteroid therapy has been the lack of long-term data. Studies with follow-up periods of 1 year or less only provide information on short-term changes in growth and may not reflect growth during a subsequent year or the ability to reach final predicted adult height. Longer

term (>1 year) studies evaluating the growth effects of nebulized budesonide inhalation suspension have not been published. However, in a prospective study, the CAMP research group compared the safety and efficacy of long-term (4–6 years) administration of inhaled budesonide by means of the Turbuhaler with that of nedocromil and placebo in 1041 children aged 5 through 12 years.⁴⁰ Skeletal maturation, determined during the last 8 months of follow-up by means of radiographic evaluation of the left wrist and hand, was used to estimate the projected final height of the patient. Although a difference in growth rates between the budesonide and placebo groups was apparent during the first year of treatment, growth rates and projected final heights were similar in all groups by end of treatment.⁴⁰ Furthermore, Agertoft and Pedersen⁶⁹ reported results of a prospective study of 142 children who were treated with daily inhaled budesonide for an average of 9.2 years (range, 3–13 years). This study found that children reached their expected final height after long-term treatment with budesonide (mean daily dose, $412 \mu\text{g}$; range, 110 – $877 \mu\text{g}$), suggesting that inhaled budesonide has no clinically important adverse effects on adult height. The growth of pediatric patients should be monitored routinely by means of the most accurate measure for the specific age group. It is important to remember that both poorly controlled asthma and inhaled corticosteroids have the potential to affect growth, and therefore growth should be carefully monitored in children with suspected asthma, irrespective of whether they are receiving corticosteroid therapy.

Clinical use

Dose and administration. For all nebulized medications, the amount of drug delivered to the lungs depends on the type of nebulizer used, the compressor performance, the patient's breathing pattern, and other variables.^{70–73} A study of 27 nebulizer-compressor combinations demonstrated that acceptable delivery of budesonide was provided in the majority of the systems tested.⁷³ Ultrasonic nebulizers are not suitable for administration of budesonide inhalation suspension because the inhaled mass of drug is decreased when suspensions are delivered from these devices.⁷² Thus budesonide inhalation suspension should be administered from a compressed air–driven jet nebulizer.

Budesonide inhalation suspension is indicated for prophylactic and maintenance therapy of asthma in patients 12 months to 8 years of age.¹⁹ Prior asthma therapy is used as a guide for determining the recommended starting dose of nebulized budesonide (Table VI).¹⁹ Budesonide inhalation suspension is effective when administered once daily, which may prove to be convenient for patients. When the desired clinical effect is achieved, the total daily dose of budesonide and the frequency of administration must be individualized for each patient, with the goal of tapering to the lowest effective dose.

For patients previously maintained on oral corticosteroids, nebulized budesonide should be started concurrently with the patient's usual maintenance dose of

systemic corticosteroid. After approximately 1 week, gradual discontinuation of the systemic corticosteroid may be initiated. Dose reductions of the systemic corticosteroid should proceed slowly, not exceeding 25% of the total dose. Further reductions may be made after 1 to 2 weeks, depending on clinical response. During discontinuation of oral corticosteroids, patients should be monitored for asthma instability (by means of pulmonary function testing) and for clinical symptoms of adrenal insufficiency, such as hypotension, joint or muscular pain, lassitude, and depression. If symptoms of adrenal insufficiency do occur, doses of systemic corticosteroids should be temporarily increased, and subsequent withdrawal should proceed more slowly.

Role in asthma management. In the National Asthma Education and Prevention Program treatment guidelines and in recently released pediatric asthma guidelines, inhaled corticosteroids are the preferred treatment for all children older than 5 years with persistent asthma (mild, moderate, or severe).^{6,18} In children 5 years of age or younger, anti-inflammatory medications are recommended for those who require symptom treatment more than 2 times per week. Although other dosage forms of budesonide are listed for use in children, the nebulized formulation of budesonide was not available in the United States when the treatment guidelines for asthma were published.^{6,18} Budesonide inhalation suspension has been available outside of the United States since 1990. Global treatment guidelines recommend budesonide as the nebulized corticosteroid for infants and young children because other inhaled corticosteroids are not available in a suitable form for nebulization.⁷⁴ Despite international adoption of these guidelines and growing support for regular use of anti-inflammatory agents, inhaled corticosteroids are still underused by many physicians, particularly in children. In a study of children requiring emergency treatment for asthma, two thirds of whom were 5 years of age or younger, only 16% of patients were reported to be using inhaled corticosteroids to control their asthma before hospitalization.⁷⁵

Three large, randomized, placebo-controlled trials in the United States have demonstrated the efficacy and safety of nebulized budesonide in pediatric patients with persistent asthma.⁵⁵⁻⁵⁷ Nebulized budesonide, administered either once or twice daily, was associated with improved asthma symptoms, decreased use of rescue medication, and improved pulmonary function. The effects of budesonide were similar across age groups and irrespective of whether the drug was administered by face mask or by mouthpiece.

Nebulized budesonide is a safe and effective treatment for maintenance and prophylaxis of persistent asthma in pediatric patients aged 12 months to 8 years and across a wide range of disease severity. The availability of nebulized budesonide enables delivery of anti-inflammatory therapy to very young asthmatic patients who may lack the coordination and understanding necessary to use metered-dose inhalers or inhalation-driven devices.

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REFERENCES

1. von Mutius E. The burden of childhood asthma. *Arch Dis Child* 2000;82(suppl II):ii2-5.
2. Weiss KB, Sullivan SD, Lyttle CS. Trends in the cost of illness for asthma in the United States, 1985-1994. *J Allergy Clin Immunol* 2000;106:493-9.
3. Kemper KJ. Chronic asthma: an update. *Pediatr Rev* 1996;17:111-7.
4. Mannino DM, Homa DM, Pertowski CA, et al. Surveillance for asthma—United States, 1960-1995. *MMWR CDC Surveill Summ* 1998; 47:1-28.
5. Centers for Disease Control and Prevention. Asthma mortality and hospitalization among children and young adults: United States, 1980-1993. *MMWR Morb Mortal Wkly Rep* 1996;45:350-3.
6. 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.
7. Blais L, Suissa S, Boivin J-F, Ernst P. First treatment with inhaled corticosteroids and the prevention of admissions to hospital for asthma. *Thorax* 1998;53:1025-9.
8. 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.
9. Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R. Inhaled steroids and the risk of hospitalization for asthma. *JAMA* 1997;277:887-91.
10. Agertoft L, Pedersen S. Importance of training for correct Turbuhaler use in preschool children. *Acta Paediatr* 1998;87:842-7.
11. Pedersen S, Hansen OR, Fuglsang G. Influence of inspiratory flow rate upon the effect of a Turbuhaler. *Arch Dis Child* 1990;65:308-19.
12. Bisgaard H, Pedersen S, Nikander K. Use of budesonide Turbuhaler in young children suspected of asthma. *Eur Respir J* 1994;7:740-2.
13. Goren A, Noviski N, Avital A, et al. Assessment of the ability of young children to use a powder inhaler device (Turbuhaler). *Pediatr Pulmonol* 1994;18:77-80.
14. Foucard T. Aggressive treatment of childhood asthma with local steroids. Good or bad? *Allergy* 1996;51:367-71.
15. Pedersen S, Frost L, Arnfred T. Errors in inhalation technique and efficiency in inhaler use in asthmatic children. *Allergy* 1986;41:118-24.
16. Möller C. Once-daily inhaled corticosteroids in children with asthma. Dry powder inhalers. *Drugs* 1999;58(suppl 4):35-41.
17. Szeffler SJ. Clinical need for a nebulized corticosteroid. *J Allergy Clin Immunol* 1999;104:S162-8.
18. American Academy of Allergy, Asthma and Immunology. Pediatric asthma: promoting best practice. Guide for managing asthma in children. Milwaukee (WI): American Academy of Allergy, Asthma & Immunology, Inc; 1999.
19. Pulmicort Respules (budesonide inhalation suspension) [prescribing information]. Wayne (PA): AstraZeneca LP; 2000.
20. Barnes PJ. Molecular mechanisms of glucocorticoid action in asthma. *Pulm Pharmacol Ther* 1997;10:3-19.
21. Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids. New developments. *Am J Respir Crit Care Med* 1998;157:S1-53.
22. Brogden RN, McTavish D. Budesonide. An updated review of its pharmacological properties, and therapeutic efficacy in asthma and rhinitis. *Drugs* 1992;44:375-407.
23. Szeffler SJ. Pharmacodynamics and pharmacokinetics of budesonide: a new nebulized corticosteroid. *J Allergy Clin Immunol* 1999;104:S175-83.
24. Miller-Larsson A, Mattsson H, Hjertberg E, Dahlbäck M, Tunek A, Brattsand R. Reversible fatty acid conjugation of budesonide. Novel mechanism for prolonged retention of topically applied steroid in airway tissue. *Drug Metab Dispos* 1998;26:623-30.
25. Tunek A, Sjödin K, Hallström G. Reversible formation of fatty acid esters of budesonide, an antiasthma glucocorticoid, in human lung and liver microsomes. *Drug Metab Dispos* 1997;25:1311-7.
26. Miller-Larsson A, Jansson P, Runström A, Brattsand R. Prolonged airway activity and improved selectivity of budesonide possibly due to esterification. *Am J Respir Crit Care Med* 2000;162:1455-61.

27. Petersen H, Kullberg A, Edsbäcker, Greiff L. Fatty acid ester formation appears to increase and prolong the retention of budesonide in human nasal mucosa in vivo as compared with fluticasone propionate [abstract]. *J Allergy Clin Immunol* 2000;105(suppl):S202.
28. Ferguson AC, Whitelaw M, Brown H. Correlation of bronchial eosinophil and mast cell activation with bronchial hyperresponsiveness in children with asthma. *J Allergy Clin Immunol* 1992;90:609-13.
29. Ferguson AC, Wong FWM. Bronchial hyperresponsiveness in asthmatic children. Correlation with macrophages and eosinophils in bronchoalveolar fluid. *Chest* 1989;96:988-91.
30. Le Bourgeois M, Goncalves M, Le Clainche L, et al. Bronchoalveolar cells in wheezy children under 3 years. *Eur Respir J* 1999;14(suppl 30):171-2.
31. Chedevergne F, Le Bourgeois M, de Blic J, Scheinmann P. The role of inflammation in childhood asthma. *Arch Dis Child* 2000;82(suppl II):ii6-9.
32. Laitinen LA, Altraja A, Karjalainen E-M, Laitinen A. Early interventions in asthma with inhaled corticosteroids. *J Allergy Clin Immunol* 2000;105:S582-5.
33. Laitinen LA, Laitinen A, Haahtela T. Airway mucosa inflammation even in patients with newly diagnosed asthma. *Am Rev Respir Dis* 1993;147:697-704.
34. Laitinen LA, Laitinen A, Haahtela T. A comparative study of the effects of an inhaled corticosteroid, budesonide, and a β_2 -agonist, terbutaline, on airway inflammation in newly diagnosed asthma: a randomized, double-blind, parallel-group controlled trial. *J Allergy Clin Immunol* 1992;90:32-42.
35. Burke CM, Sreenan S, Power CK, Pathmakanthan S, Poulter LW. Mechanism of action of inhaled corticosteroids in bronchial asthma: a controlled study [abstract]. *Eur Respir J* 1994;7(suppl 18):421S.
36. Barnes PJ. New concepts in the pathogenesis of bronchial hyperresponsiveness and asthma. *J Allergy Clin Immunol* 1989;83:1013-26.
37. Holgate ST, Beasley R, Twentyman OP. The pathogenesis and significance of bronchial hyperresponsiveness in airways disease. *Clin Sci* 1987;73:561-72.
38. Juniper EF, Kline PA, Vanzieleghe MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. *Am Rev Respir Dis* 1990;142:832-6.
39. Toogood JH, Frankish CW, Jennings BH, et al. A study of the mechanism of the antiasthmatic action of inhaled budesonide. *J Allergy Clin Immunol* 1990;85:872-80.
40. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343:1054-63.
41. Agertoft L, Andersen A, Weibull E, Pedersen S. Systemic availability and pharmacokinetics of nebulized budesonide in preschool children. *Arch Dis Child* 1999;80:241-7.
42. Brattsand R, Källström L, Nilsson E, Ryrfeldt Å, Tönnesson M. The lung disposition of budesonide in guinea pig and rat. *Eur J Respir Dis* 1982;63(suppl 122):263-5.
43. Crim C, Pierre LN, Daley-Yates PT. A review of the pharmacology and pharmacokinetics of inhaled fluticasone propionate and mometasone furoate. *Clin Ther* 2001;23:1339-54.
44. Daley-Yates PT, Price AC, Sisson JR, Pereira A, Dallow N. Beclomethasone dipropionate: absolute bioavailability, pharmacokinetics and metabolism following intravenous, oral, intranasal and inhaled administration in man. *Br J Clin Pharmacol* 2001;52:400-9.
45. Bessmerly O, Liang J, Hochhaus G, Chesrown S, Hendeles L. Fluticasone plasma concentrations in children with asthma after delivery by MDI. *J Pediatr Pharmacol Ther* 2001;6:212-7.
46. Thorsson L, Edsbäcker S, Conradson T-B. Lung deposition of budesonide from Turbuhaler is twice that from a pressurized metered-dose inhaler P-MDI. *Eur Respir J* 1994;7:1839-44.
47. Jönsson G, Åström A, Andersson P. Budesonide is metabolized by cytochrome P450 3A (CYP3A) enzymes in human liver. *Drug Metab Dispos* 1995;23:137-42.
48. Andersson P, Ryrfeldt Å. Biotransformation of the topical glucocorticoids budesonide and beclomethasone 17 α ,21-dipropionate in human liver and lung homogenate. *J Pharm Pharmacol* 1984;36:763-5.
49. Dahlberg E, Thalén A, Brattsand R, et al. Correlation between chemical structure, receptor binding, and biological activity of some novel, highly active, 16 α , 17 α -acetal-substituted glucocorticoids. *Mol Pharmacol* 1984;25:70-8.
50. Edsbäcker S, Andersson P, Lindberg C, Paulson J, Ryrfeldt Å, Thalén A. Liver metabolism of budesonide in rat, mouse, and man. Comparative aspects. *Drug Metab Dispos* 1987;15:403-11.
51. de Blic J, Delacourt C, Le Bourgeois M, et al. Efficacy of nebulized budesonide in treatment of severe infantile asthma: a double-blind study. *J Allergy Clin Immunol* 1996;98:14-20.
52. Hvizdos KM, Jarvis B. Budesonide inhalation suspension: a review of its use in infants, children and adults with inflammatory respiratory disorders. *Drugs* 2000;60:1141-78.
53. 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 18):27S.
54. Ilangoan P, Pedersen S, Godfrey S, Nikander K, Noviski N, Warner JO. Treatment of severe steroid dependent preschool asthma with nebulized budesonide suspension. *Arch Dis Child* 1993;68:356-9.
55. Wennergren G, Nordvall SL, Hedlin G, Möller C, Wille S, Åsbrink Nilsson E. Nebulized budesonide for the treatment of moderate to severe asthma in infants and toddlers. *Acta Paediatr* 1996;85:183-9.
56. Pedersen S, Ramsgaard-Hansen O, Nikander K. Budesonide suspension for nebulisation in children with asthma [abstract]. *Eur Respir J* 1989;2(suppl 8):647S.
57. Baker JW, Mellon M, Wald J, Welch M, Cruz-Rivera M, Walton-Bowen K. A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants. *Pediatrics* 1999;103:414-21.
58. Kemp JP, Skoner DP, 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.
59. 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.
60. Mendelson L, Cook D, Cruz-Rivera M, Fitzpatrick S, Smith JA. Twice daily budesonide inhalation suspension in infants and children <4 and $\geq$ 4 years of age with persistent asthma. *J Asthma* 2002. In press.
61. Scott MB, Ellis MH, Cruz-Rivera M, Walton-Bowen K, Fitzpatrick S, Smith JA. Once-daily budesonide inhalation suspension in infants and children <4 and $\geq$ 4 years of age with persistent asthma. *Ann Allergy Asthma Immunol* 2001;87:488-95.
62. Lowenthal D, Kattan M. Facemasks versus mouthpieces for aerosol treatment of asthmatic children. *Pediatr Pulmonol* 1992;14:192-6.
63. Georgitis JW, McWilliams B, Cruz-Rivera M, Fitzpatrick S, Smith JA. Effective once-daily administration of budesonide inhalation suspension by nebulizer with facemasks or mouthpieces for persistent asthma in infants and young children. *Pediatr Asthma Allergy Immunol* 2001;15:3-13.
64. Mellon M, Leflein J, Walton-Bowen K, Cruz-Rivera M, Fitzpatrick S, Smith JA. Comparable efficacy of administration with face mask or mouthpiece of nebulized budesonide inhalation suspension for infants and young children with persistent asthma. *Am J Respir Crit Care Med* 2000;162:593-8.
65. Guyatt GH, Juniper EF, Walter SD, Griffith LE, Goldstein RS. Interpreting treatment effects in randomised trials. *BMJ* 1998;316:690-3.
66. Scott MB, Skoner DP. Short-term and long-term safety of budesonide inhalation suspension in infants and young children with persistent asthma. *J Allergy Clin Immunol* 1999;104:S200-9.
67. Skoner DP, Szeffler SJ, Welch M, Walton-Bowen K, Cruz-Rivera M, Smith JA. Longitudinal growth in infants and young children treated with budesonide inhalation suspension for persistent asthma. *J Allergy Clin Immunol* 2000;105:259-68.
68. Szeffler S, Fitzpatrick S, Cruz-Rivera M, Lyzell E. Lack of cataracts and other localized adverse events in children treated with nebulized Pulmicort Respules (budesonide inhalation suspension) [abstract]. *Am J Respir Crit Care Med* 2001;163:A589.
69. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med* 2000;343:1064-9.
70. Barry PW, O'Callaghan C. Nebuliser therapy in childhood. *Thorax* 1997;52(suppl 2):S78-88.
71. Barry PW, O'Callaghan C. An in vitro analysis of the output of budesonide from different nebulizers. *J Allergy Clin Immunol* 1999;104:1168-73.

72. Nikander K, Turpeinen M, Wollmer P. The conventional ultrasonic nebulizer proved inefficient in nebulizing a suspension. *J Aerosol Med* 1999;12:47-53.
73. Smaldone GC, Cruz-Rivera M, Nikander K. In vitro determination of inhaled mass and particle distribution for budesonide nebulizing suspension. *J Aerosol Med* 1998;11:113-25.
74. National Heart, Lung, and Blood Institute. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention NHLBI/WHO Workshop Report. Bethesda (MD): National Institutes of Health; 1995. NIH publication no. 95-3659.
75. Friday GA Jr, Khine H, Lin MS, Caliguiri LA. Profile of children requiring emergency treatment for asthma. *Ann Allergy Asthma Immunol* 1997;78:221-4.