Comparable Efficacy of Administration with Face Mask or Mouthpiece of Nebulized Budesonide Inhalation Suspension for Infants and Young Children with Persistent Asthma

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A randomized, double-blind, placebo-controlled, parallel-group study including 481 children at 37 centers in the United States demonstrated the efficacy and safety of budesonide inhalation suspension in doses of 0.25 mg once daily, 0.25 mg twice daily, 0.5 mg twice daily, and 1.0 mg daily in infants and young children with persistent asthma. The retrospective analysis presented here compares the efficacy of treatment with the suspension administered through a face mask or mouthpiece. All patients receiving budesonide inhalation suspension via face mask or mouthpiece showed clinical improvements in nighttime and daytime asthma symptoms as compared with administration of a placebo. The improvements were of similar magnitude as those observed in an analysis of all patients treated. Improvements in nighttime asthma symptoms were statistically significant with budesonide at 0.25 mg daily ($p = 0.040$), 0.25 mg twice daily ($p = 0.008$), and 0.5 mg twice daily ($p = 0.046$) delivered by face mask. In patients using mouthpieces, nighttime asthma symptoms improved significantly in the 0.25-mg twice-daily ($p = 0.005$) and 1.0-mg daily ($p = 0.035$) groups. Patients receiving budesonide at 0.5 mg twice daily via a face mask improved significantly in daytime asthma symptoms ($p = 0.009$). The use of breakthrough medication was reduced in patients receiving budesonide via face masks or mouthpieces relative to placebo, and treatment was well tolerated in all study groups. This retrospective analysis suggests that nebulized budesonide inhalation suspension can be administered effectively by either face mask or mouthpiece to young children with persistent asthma.

Asthma causes significant morbidity and mortality in children, affecting an estimated 4.8-million children in the United States (1, 2). Although asthma is now recognized as an inflammatory disease, antiinflammatory agents are underutilized in its treatment (3). Until recently, asthma therapy for infants and young children was limited to oral and nebulized formulations of bronchodilators, cromolyn sodium, and oral corticosteroids. Recent evidence suggests that the duration of asthma in children may be associated with a lower level of lung function and more asthma symptomatology (4), and that early intervention with antiinflammatory medications, including inhaled glucocorticosteroids, may prevent the development of irreversible airway obstruction (5–7). A recent study by Clough and colleagues (8) identified factors predictive of persistence of wheezing in infants; these findings will contribute to studies of early intervention strategies. Furthermore, recent guidelines for asthma treatment from the National Heart, Lung, and Blood Institute (NHLBI) and the pediatric initiative of the American Academy of Allergy, Asthma, and Immunology recommend inhaled antiinflammatory agents for all but the mildest cases of asthma (1, 9).

An estimated 80% of children with asthma present with symptoms within the first 2 yr of life (10). The efficacy of inhaled budesonide in alleviating symptoms of asthma has been demonstrated in numerous trials in children under 4 yr of age with a pressurized metered-dose inhaler (pMDI) with a spacer and face mask (11–13).

Large-volume pMDIs with a spacer device and face mask are usually recommended initially for young children (1), but may require the assistance of more than one adult for drug administration (14). Use of smaller-volume pMDIs may improve ease of handling, but a decline in performance has been observed (15). Generally, children under 4 yr of age lack the coordination necessary to use pMDI devices (1, 16), and in one study, nearly one-third of pediatric patients experienced some difficulty in accepting a metered-dose inhaler with a spacer (13). Nebulizer treatment, however, permits drug delivery to young children through passive inhalation (1). Currently, there are no approved inhaled corticosteroids available in the United States for nebulization or for use in children under 4 yr of age.

Budesonide inhalation suspension (Pulmicort Respules; AstraZeneca, Wayne, PA) is a novel nebulized corticosteroid that will soon be available in the United States for use in infants and children 1 to 8 yr of age who have persistent asthma. A number of small trials or individual case studies have shown that nebulized budesonide reduces asthma symptoms in infants and children (17–21). In a recent series of randomized, double-blind, placebo-controlled trials, the efficacy and safety of budesonide inhalation suspension were demonstrated at various doses and with various administration schedules for the treatment of mild to moderate asthma in infants and young children with disease meeting well-defined criteria (22–24). This report presents the results of a retrospective analysis of one of these randomized trials (22). This retrospective analysis compared the efficacy of nebulized budesonide administered via face mask with that administered via a mouthpiece.

METHODS

Patients

A parallel-group, double-blind, placebo-controlled study involving 481 randomized patients was conducted at 37 centers in the United States. Children 6 mo to 8 yr of age who had moderate, persistent asthma diagnosed according to the NHLBI criteria (25) were enrolled in the study. Patients were required to have a 6-mo history of recurrent exacerbations of cough and/or wheezing (which could include nighttime symptoms), with infrequent severe exacerbations. Other eligibility criteria included the presence of asthma symptoms (with an

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more of the 7 d immediately preceding randomization, daily use of at least one chronic asthma medication (e.g., an inhaled corticosteroid, cromolyn sodium, or theophylline) for at least 3 mo before screening, and the periodic use of rescue bronchodilator therapy for breakthrough asthma symptoms. Patients who were capable of consistently performing pulmonary function tests (PFTs) were required to demonstrate a baseline $FEV_1 \geq 50\%$ predicted (26) and a reversibility of $\geq 15\%$ at 15 ± 5 min after a standard dose of inhaled albuterol.

Patients were excluded from the study for any of the following reasons: history of severe and/or unstable asthma, long-term use of systemic corticosteroids within 12 wk of screening, or a history of intermittent use of systemic corticosteroids within 30 d of screening. Prior use of an inhaled corticosteroid was permitted if it was used daily for at least 2 mo at a stable dose before screening. Patients with other concomitant lung diseases and patients hospitalized for treatment of airway obstruction within 30 d of screening were excluded, as were patients with upper or lower respiratory tract infections within 14 d of screening.

Study Design

Informed consent was obtained from the patient and/or parent or guardian at the initial screening visit. A 2- to 3-wk baseline period preceded the 12-wk treatment period. Patients visited their respective study sites six times: at screening, at randomization, and after 2, 4, 8, and 12 wk of study therapy. Each clinic visit included a brief physical examination and a review of daily diary records; spirometry was done in the subset of patients who were capable of consistently performing the necessary maneuvers. Diary cards were used to record the severity of nighttime and daytime asthma symptoms, morning and evening peak expiratory flow rates (PEFRs), and bronchodilator use for breakthrough symptoms. A four-point asthma symptom score scale was used to determine asthma severity, on which 0 = no symptoms of asthma, 1 = mild symptoms (awareness of asthma symptoms and/or signs that are easily tolerated), 2 = moderate symptoms (asthma symptoms and/or signs with some discomfort, causing some interference with daily activities or sleep), and 3 = severe symptoms (incapacitating asthma symptoms or signs with inability to perform daily activities or to sleep). Morning and evening PEFRs were measured with a peak flow meter (Vitalograph, Inc., Lenexa, KS) in the subset of patients capable of consistently performing peak flow measurement maneuvers.

After the baseline period, eligible patients discontinued their chronic asthma medications and were randomized to receive nebulized placebo or one of the following nebulized treatment regimens: budesonide in a dose of 0.25 mg daily, 0.25 mg twice daily, 0.5 mg twice daily, or 1.0 mg daily. Budesonide inhalation suspension and placebo were supplied in identical 2.0-ml white polyethylene ampules, and a Pari LC-Jet Plus nebulizer with a mouthpiece or face mask and Pari Master compressor (Pari Respiratory Equipment, Inc., Richmond, VA) were used to deliver the medication. Face masks and mouthpieces were issued to patients on the basis of their demonstrated ability to use them. The time for complete nebulization was approximately 5 min. Vitalograph peak flow meters were issued to the subset of children who could perform this test, and these patients and their parents or guardians were instructed about the meter's use and care.

The incidence and severity of adverse events (AEs) were recorded during the study. AEs were defined as any unintended, unfavorable clinical signs, symptoms, medical complaints, or clinically relevant changes in laboratory test values. Assessment was conducted by means of standard questioning of patients and/or legal guardians, and by review of clinical and laboratory test results. AEs were classified by the patients' parents or legal guardians as mild (easily tolerated symptoms), moderate (enough discomfort to interfere with daily life/usual activities), or severe (incapacitating, such as the inability to attend day care/school or to take part in normal activities). Safety variables included changes in physical examination findings, vital signs, and clinical laboratory tests. Changes in adrenocorticotropic hormone-stimulated plasma cortisol levels from baseline to the end of the 12-wk study period were measured in a subset of patients at selected study sites to assess adrenal function. These data are reported elsewhere (22).

Data Analysis

Changes from baseline values (mean of the last 7 d preceding the randomization) in study (mean over Weeks 0 to 12) were analyzed for all efficacy variables (except spirometry measurements, for which mean values over Weeks 2 to 12 were calculated). Data were included from all patients who received at least one dose of medication during the treatment phase and who had at least one observation while receiving study medication. Data were carried forward for patients who discontinued study participation or had missing observations. The primary efficacy variables were changes from baseline in nighttime and daytime asthma symptom scores. Secondary efficacy variables included the change from baseline in number of days per 2-wk interval on which rescue medications were used, morning and evening PEFRs and spirometric test results (in the subset of patients who could perform the tests), and the proportion of patients who were withdrawn from the study. The proportion of patients withdrawn from the study was evaluated with Fisher's exact test; all other efficacy variables were evaluated through analysis of variance (ANOVA) techniques. The statistical analysis presented here to compare the efficacy of face mask versus mouthpiece administration of budesonide was a retrospective analysis. The continuing demand for safe, cost-effective medical treatments has brought an increased reliance on different types of clinical data, including retrospective analyses of previous clinical trial data or data from small-scale case or cohort studies (27). Retrospective analyses may be useful in identifying unsuspected findings or associations, development of new hypotheses, or addition of constructive input into prospective studies (27). However, limitations may be present in measurement capabilities, as in our analysis, in which study groups were further stratified after the study period was completed. The sample size of the original study design provided power to detect differences in efficacy for the different budesonide dose groups versus placebo. For this analysis, emphasis was placed on the magnitude of differences in each of the study variables in the group using face masks and that using mouthpieces. The Statistical Analysis Systems (SAS) statistical software package version 6.11 (SAS Institute, Inc., Cary, NC) was used for statistical analysis.

RESULTS

Four hundred seventy-one patients were included in the all-patients-treated analysis; a face mask was used in the treatment of 211 patients and a mouthpiece was used in the treatment of 260 patients. Baseline demographic characteristics and baseline asthma symptoms and pulmonary function for children who received budesonide inhalation suspension and placebo are listed in Tables 1 and 2. As expected, most of the younger patients used face masks during nebulization. The mean age of face mask users was 36.4 mo and that of mouthpiece users was 70.0 mo. Among the 214 patients < 4 yr of age, 161 (75%) used a face mask and 53 (25%) used a mouthpiece; 50 of 257 patients ≥ 4 yr of age used a face mask (19%) and 207 (81%) used a mouthpiece. Other differences between the study groups in baseline characteristics were consistent with the older age of patients who used a mouthpiece; differences included duration of asthma and fraction of children capable of consistently performing PFTs. The average duration of asthma in patients using face masks was 24.3 mo and that in patients using mouthpieces was 42.0 mo. Only 13 of 211 patients (6.2%) treated with face masks were capable of performing consistent PFTs, as compared with 148 of 260 patients (56.9%) using mouthpieces.

Baseline nighttime and daytime asthma symptom scores were well balanced between the groups of children who received treatment with face masks and those using mouthpieces. The average nighttime asthma symptom score was 1.21 for patients who used face masks and 1.22 for patients who used mouthpieces. Similarly, patients who received treatment with face masks had an average daytime symptom score of 1.31 as compared with an average score of 1.26 among patients using mouthpieces.

Of the 211 patients receiving treatment with face masks

TABLE 1

BASELINE DEMOGRAPHICS OF STUDY POPULATION

Characteristic	Face Mask Budesonide Inhalation Suspension					Mouthpiece Budesonide Inhalation Suspension				
	Placebo (*n* = 35)	0.25 mg Daily (*n* = 49)	0.25 mg Twice Daily (*n* = 43)	0.5 mg Twice Daily (*n* = 44)	1.0 mg Daily (*n* = 40)	Placebo (*n* = 57)	0.25 mg Daily (*n* = 44)	0.25 mg Twice Daily (*n* = 54)	0.5 mg Twice Daily (*n* = 52)	1.0 mg Daily (*n* = 53)
Sex, n (%)										
Male	25 (71.4%)	36 (73.5%)	24 (55.8%)	34 (77.3%)	27 (67.5%)	32 (56.1%)	22 (50.0%)	37 (68.5%)	33 (63.5%)	34 (64.2%)
Female	10 (28.6%)	13 (26.5%)	19 (44.2%)	10 (22.7%)	13 (32.5%)	25 (43.9%)	22 (50.0%)	17 (31.5%)	19 (36.5%)	19 (35.8%)
Age, mo										
Mean ± SD	39.7 ± 22.8	38.9 ± 17.5	34.5 ± 20.5	35.5 ± 16.8	33.7 ± 17.4	68.9 ± 22.1	71.3 ± 20.9	70.3 ± 20.3	67.8 ± 24.1	71.9 ± 21.7
Range	11–89	8–83	7–95	9–86	8–71	19–100	34–107	22–105	10–107	17–108
Race, n (%)										
White	31 (88.6%)	37 (75.5%)	31 (72.1%)	35 (79.5%)	30 (75.0%)	48 (84.2%)	35 (79.5%)	44 (81.5%)	45 (86.5%)	46 (86.8%)
Black	3 (8.6%)	10 (20.4%)	11 (25.6%)	8 (18.2%)	7 (17.5%)	4 (7.0%)	7 (15.9%)	6 (11.1%)	3 (5.8%)	2 (3.8%)
Hispanic	1 (2.9%)	1 (2.0%)	1 (2.3%)	—	2 (5.0%)	3 (5.3%)	2 (4.5%)	2 (3.7%)	3 (5.8%)	3 (5.7%)
Asian	—	—	—	—	—	1 (1.8%)	—	—	—	1 (1.9%)
Other	—	1 (2.0%)	—	1 (2.3%)	1 (2.5%)	1 (1.8%)	—	2 (3.7%)	1 (1.9%)	1 (1.9%)
Duration of asthma, mo										
Mean ± SD	28.9 ± 20.7	24.8 ± 15.7	23.0 ± 19.0	22.2 ± 14.0	23.5 ± 13.8	40 ± 23.7	43.4 ± 24.1	39.6 ± 23.5	43.3 ± 24.2	44.2 ± 26.4
Range	6–78	5–68	4–83	5–65	6–60	5–90	2–91	4–96	7–88	8–98

the placebo group, 38 (78%) patients in the group given budesonide at 0.25 mg daily, 33 (77%) patients in the group given budesonide at 0.25 mg twice daily, 35 (80%) patients in the group given budesonide at 0.5 mg twice daily, and 24 (60%) patients in the group given budesonide at 1.0 mg daily. Among the patients who used mouthpieces, 206 of 260 (79%) completed the study, including 39 (68%) patients in the placebo group, 36 (82%) patients in the group given budesonide at 0.25 mg daily, 45 (83%) patients in the group given budesonide at 0.25 mg twice daily, 44 (85%) patients in the group given budesonide at 0.5 mg twice daily, and 42 (79%) patients in the group given budesonide at 1.0 mg daily. Differences in the proportions of mouthpiece users and face mask users who completed the study were not statistically significant. Among face mask users, reasons for study discontinuation included nonprotocol use of medications (23%), AEs (2%), disease deterioration (< 1%), noncompliance with study procedures (< 1%), withdrawal of consent (< 1%), ineligibility (< 1%), and loss to follow-up (< 1%). Among mouthpiece users, reasons for study discontinuation included nonprotocol use of medications (15%), disease deterioration (3%), noncompliance with study procedures (1%), AEs (< 1%), withdrawal of consent (< 1%), and ineligibility (< 1%). The proportion of treatment discontinuations caused by worsening asthma did not differ significantly between the placebo group and any of the budesonide inhalation suspension treatment groups. In addition, no significant differences were

TABLE 2

BASELINE ASTHMA SYMPTOMS AND PULMONARY FUNCTION OF STUDY POPULATION

Variable	Face Mask Budesonide Inhalation Suspension					Mouthpiece Budesonide Inhalation Suspension				
	Placebo (*n* = 35)	0.25 mg Daily (*n* = 49)	0.25 mg Twice Daily (*n* = 43)	0.5 mg Twice Daily (*n* = 44)	1.0 mg Daily (*n* = 40)	Placebo (*n* = 57)	0.25 mg Daily (*n* = 44)	0.25 mg Twice Daily (*n* = 54)	0.5 mg Twice Daily (*n* = 52)	1.0 mg Daily (*n* = 53)
Nighttime asthma symptom scores*										
n	35	49	43	44	40	57	44	54	52	53
Mean ± SD	1.16 ± 0.69	1.18 ± 0.60	1.33 ± 0.67	1.19 ± 0.64	1.22 ± 0.65	1.17 ± 0.61	1.08 ± 0.53	1.33 ± 0.62	1.22 ± 0.61	1.27 ± 0.62
Daytime asthma symptom scores*										
n	35	48	43	44	40	57	44	54	52	53
Mean ± SD	1.33 ± 0.52	1.27 ± 0.53	1.32 ± 0.48	1.39 ± 0.52	1.24 ± 0.57	1.24 ± 0.48	1.16 ± 0.34	1.30 ± 0.50	1.29 ± 0.52	1.31 ± 0.57
FEV_1, L										
n	2	4	2	1	3	29	28	32	28	31
% predicted ± SD†	65.0 ± 25.5	72.3 ± 24.3	82.5 ± 23.3	90.0	75.3 ± 27.6	80.0 ± 16.5	80.1 ± 15.8	83.1 ± 20.6	81.6 ± 18.0	78.8 ± 13.5
n	3	4	2	1	3	29	28	32	28	32
% reversibility ± SD	26.7 ± 3.8	33.0 ± 18.9	19.0 ± 4.2	40.0	25.3 ± 9.3	29.4 ± 19.0	28.1 ± 15.3	31.2 ± 16.8	29.7 ± 19.4	26.8 ± 12.2
Evening PEFR, L/min										
n	3	4	2	1	3	29	28	32	28	31
Mean ± SD	135.2 ± 32.4	129.4 ± 23.5	187.5 ± 95.5	170.0	119.1 ± 36.6	163.4 ± 37.1	175.6 ± 52.2	167.5 ± 33.1	176.9 ± 54.5	170.8 ± 33.4
Morning PEFR, L/min										
n	3	4	2	1	3	29	28	32	28	31
Mean ± SD	133.6 ± 34.7	125.3 ± 18.7	166.2 ± 71.4	162.9	107.9 ± 42.1	158.2 ± 38	169.7 ± 55.0	156.6 ± 32.2	167.0 ± 49.7	161.4 ± 37.9

observed in any treatment group between patients who received treatment with face masks and those treated with mouthpieces.

Efficacy

Adjusted mean changes in nighttime and daytime asthma symptom scores from baseline to the 12-wk treatment period are shown in Figures 1 and 2. Overall, mean changes in nighttime or daytime asthma symptom scores with face mask use were numerically similar to those observed with use of a mouthpiece. The improvements also were of similar magnitude to those observed in the total patient population (22). In the retrospective analysis, the improvements in nighttime asthma symptoms were statistically significant with budesonide delivered by face mask at 0.25 mg daily ($p = 0.040$), 0.25 mg twice daily ($p = 0.008$), and 0.5 mg twice daily ($p = 0.046$) (Figure 1). Among mouthpiece users, significant differences from placebo in nighttime asthma symptoms were observed in patients who received nebulized budesonide at 0.25 mg twice daily ($p = 0.005$) and 1.0 mg daily ($p = 0.035$). Significant differences in changes in daytime symptom scores versus placebo were observed in the group of face mask users who received budesonide at 0.5 mg twice daily ($p = 0.009$) (Figure 2).

Differences in changes in nighttime asthma symptom scores over the 12-wk study period for patients using mouthpieces relative to those using face masks were 0.22 ± 0.16 for the placebo group, 0.04 ± 0.12 for the group treated with budesonide at 0.25 mg daily, 0.02 ± 0.13 for the group treated with budesonide at 0.25 mg twice daily, 0.01 ± 0.14 for the group treated with budesonide at 0.5 mg twice daily, and 0.06 ± 0.13 for the group treated with budesonide at 1.0 mg daily. The corresponding differences in changes in daytime asthma symptom scores for mouthpiece users relative to face mask users were 0.12 ± 0.13 in the placebo group, 0.08 ± 0.12 in the group treated with budesonide at 0.25 mg daily, -0.02 ± 0.12 in the group treated with budesonide at 0.25 mg twice daily, 0.10 ± 0.13 in the group treated with budesonide at 0.5 mg twice daily, and -0.03 ± 0.13 in the group treated with budesonide at 1.0 mg daily. Therefore, the overall changes in symptom scores were very similar among face mask users and mouthpiece users.

An overall reduction in the use of breakthrough medications was observed in all budesonide inhalation suspension treatment groups for both face mask and mouthpiece users.

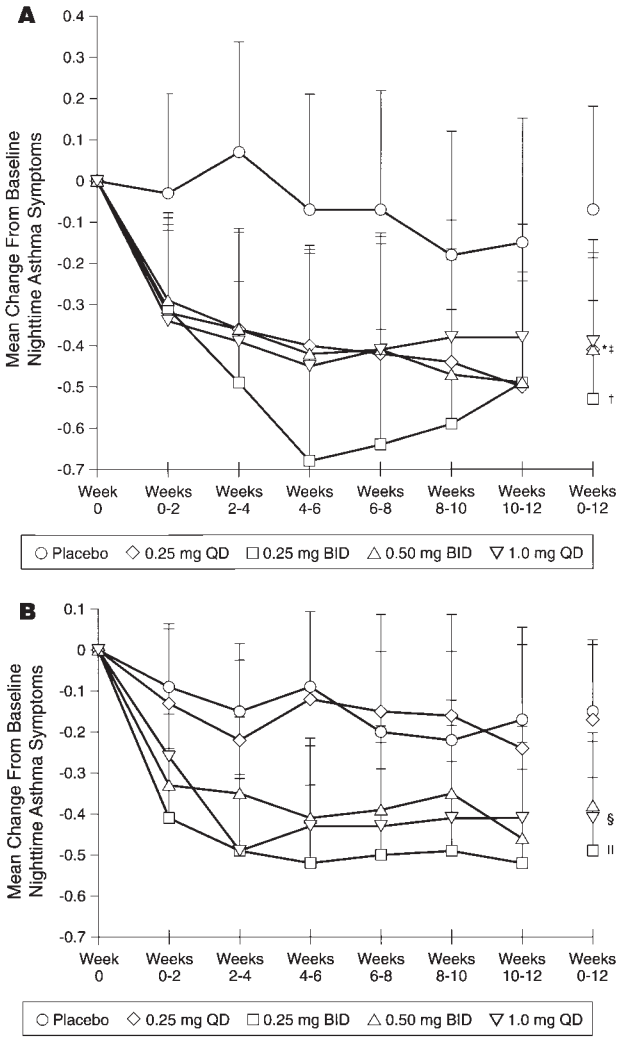

Figure 1. Adjusted mean changes from baseline in nighttime asthma symptom scores for patients using face masks (*A*) and mouthpieces (*B*). *$p = 0.04$ for budesonide at 0.25 mg daily versus placebo; †$p = 0.008$ for budesonide at 0.25 mg twice daily versus placebo; ‡$p = 0.046$ for budesonide at 0.5 mg twice daily versus placebo; §$p = 0.005$ for budesonide at 1.0 mg daily versus placebo; ‖$p = 0.035$ for budes-

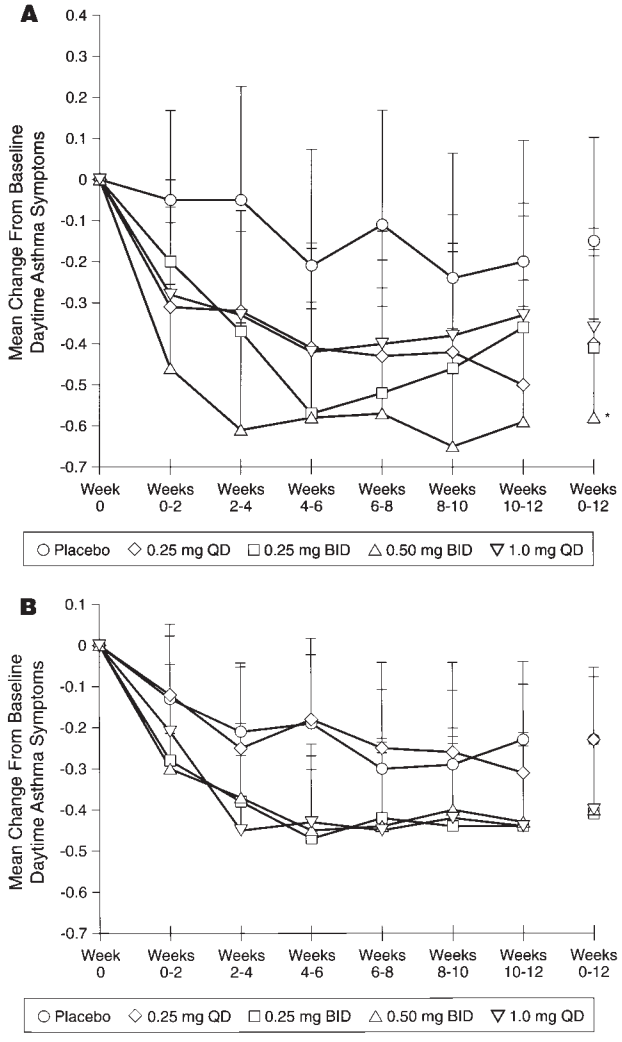

Figure 2. Adjusted mean changes from baseline in daytime asthma symptom scores for patients using face masks (*A*) and mouthpieces

The number of days of breakthrough medication use per 2-wk interval decreased significantly in patients treated with budesonide inhalation suspension taken by mouthpiece as compared with those who received placebo ($p \leq 0.008$ for all dose groups). Among mouthpiece users, differences in changes in days per 2-wk interval on which patients took breakthrough medications relative to placebo were −3.09 d ($p = 0.008$) for the group treated with budesonide at 0.25 mg daily, −3.78 d ($p = 0.001$) for the group treated with budesonide at 0.25 mg twice daily, −4.26 d ($p < 0.001$) for the group treated with budesonide at 0.5 mg twice daily, and −3.55 d ($p = 0.001$) for the group treated with budesonide at 1.0 mg daily (Figure 3). Patients who received budesonide through face masks also reported use of less breakthrough medication per 2-wk interval than did those who received placebo, with differences of −1.17 d in the group given budesonide at 0.25 mg daily, −1.29 d in the group given budesonide at 0.25 mg twice daily, −0.87 d in the group given budesonide at 0.5 mg twice daily, and −0.35 d in the group given budesonide at 1.0 mg daily. These reductions were not statistically significant, which may be explained by the small sample size and by the fact that this group of patients generally was younger and perhaps less likely to request breakthrough medications. When the number of days of use per 2-wk interval of breakthrough medications by mouthpiece users was compared with that by face mask users within each dose group, however, there were no statistically significant differences between these patient groups.

Most patients who received treatment with face masks were unable to reproducibly perform PFTs. Consequently, these additional measures of efficacy were meaningful only in patients who used mouthpieces. Clinically significant improvements in PFTs were observed in patients who used mouthpieces for nebulization; improvements in FEV_1, FVC, and evening PEFR achieved statistical significance ($p = 0.039$, $p = 0.005$, and $p = 0.023$, respectively) in the group treated with budesonide at 0.5 mg twice daily as compared with the placebo group.

Safety

The overall incidence, type, and severity of non-asthma–related AEs were similar in the placebo and budesonide inhalation suspension treatment groups (Table 3). The most frequently reported AEs among all treatment groups were respiratory infection, fever, sinusitis, otitis media, and rhinitis. No clinically significant differences were observed between the budesonide inhalation suspension and placebo groups in vital signs, physical examination findings, or laboratory tests (including nasal or oral fungal cultures) during the course of the study. The overall incidence of any AEs among budesonide-treated patients was slightly higher in patients who received treatment with face masks (85%) than in those who received treatment with mouthpieces (78%).

TABLE 3

ADVERSE EVENTS EXPERIENCED BY ⩾ 5% OF PATIENTS IN PLACEBO VERSUS ALL TREATMENT GROUPS FOR FACE MASK AND MOUTHPIECE USERS

	Face Mask		Mouthpiece	
Adverse Event	Placebo (*n = 35*) n (%)	BIS (*n = 176*) n (%)	Placebo (*n = 57*) n (%)	BIS (*n = 203*) n (%)
Respiratory infection	11 (31)	73 (41)	16 (28)	62 (31)
Fever	6 (17)	48 (27)	13 (23)	22 (11)
Sinusitis	4 (11)	30 (17)	14 (25)	25 (12)
Otitis media	8 (23)	32 (18)	7 (12)	17 (8)
Rhinitis	3 (9)	24 (14)	6 (11)	15 (7)
Bronchitis	—	5 (3)	7 (12)	7 (3)
Headache	1 (3)	9 (5)	7 (12)	10 (5)
Bronchospasm	4 (11)	10 (6)	5 (9)	5 (2)
Accident and/or injury	1 (3)	13 (7)	6 (11)	16 (8)
Coughing	3 (9)	9 (5)	4 (7)	14 (7)
Gastroenteritis	3 (9)	7 (4)	3 (5)	16 (8)
Moniliasis	—	12 (7)	2 (4)	6 (3)
Pharyngitis	2 (6)	2 (1)	3 (5)	13 (6)
Pneumonia	—	4 (2)	3 (5)	2 (1)
Viral infection	2 (6)	8 (5)	1 (2)	10 (5)
Vomiting	1 (3)	11 (6)	1 (2)	4 (2)
Ear infection NOS	1 (3)	11 (6)	2 (4)	7 (3)
Diarrhea	—	8 (5)	1 (2)	3 (1)

Definition of abbreviations: BIS = Budesonide inhalation suspension; NOS = not otherwise specified.

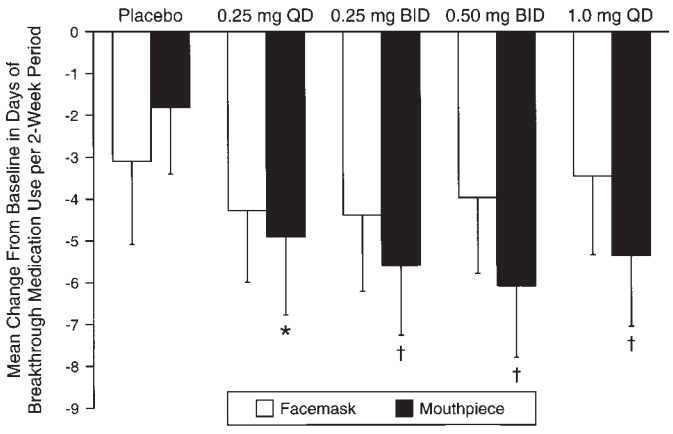

Figure 3. Adjusted mean changes from baseline in days per 2-wk interval of breakthrough medication use. *p = 0.0008 for budesonide at 0.25 mg daily versus placebo; †p ⩽ 0.001 for budesonide at 0.25 mg

DISCUSSION

This study showed that budesonide inhalation suspension at 0.25 mg twice daily, 0.5 mg twice daily, and 1.0 mg daily resulted in improvements in all efficacy parameters in infants and young children with moderate persistent asthma (22). The retrospective analysis presented here compared face mask versus mouthpiece administration of budesonide, and evaluated efficacy on the basis of symptom scores and breakthrough medication use. This analysis indicated that treatment at the foregoing dose levels of budesonide inhalation suspension alleviated nighttime and daytime asthma symptoms and reduced the use of breakthrough medication in both children using face masks and in those using mouthpieces. The mode of administration apparently does not affect the efficacy of budesonide treatment.

Young children with asthma may be unable to use dry powder or pMDI administration devices; for these patients, nebulization may be the preferred route of inhaled drug administration. Zainudin and colleagues (28) compared various methods of administration and found that the amount of an inhaled bronchodilator deposited in the lungs by a pMDI device was not significantly different from the amount deposited by a nebulizer. Three randomized, placebo-controlled studies determined that administration of budesonide by nebulizer is effective in the treatment of infants and young children with asthma (22–24).

Nebulizer treatment with a face mask is a reliable means of delivering aerosols. In two small studies of β_2-agonists in asthmatic patients, no difference in response to treatment was

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