

A COMPARISON OF LOW-DOSE INHALED BUDESONIDE PLUS THEOPHYLLINE AND HIGH-DOSE INHALED BUDESONIDE FOR MODERATE ASTHMA

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ABSTRACT

Background Inhaled glucocorticoids and oral theophylline are widely used to treat asthma. We compared the benefits of adding theophylline to inhaled glucocorticoid with those of doubling the dose of inhaled glucocorticoid in patients with persistent symptoms despite the use of inhaled glucocorticoid.

Methods In a double-blind, placebo-controlled trial, we randomly assigned 62 patients to receive either 400 μg of inhaled budesonide (low-dose budesonide) with 250 or 375 mg of theophylline (depending on body weight) or 800 μg of inhaled budesonide (high-dose budesonide). All doses were given twice daily for three months. Lung function was measured serially, and patients kept records of peak expiratory flow, symptoms, and albuterol use. The effects of treatment on endogenous cortisol levels were also assessed.

Results Both treatments resulted in improvements in lung function that were sustained throughout the study. As compared with treatment with high-dose budesonide, treatment with low-dose budesonide plus theophylline resulted in greater improvements in forced vital capacity ($P=0.03$) and forced expiratory volume in one second ($P=0.03$). There were significant and similar reductions in β_2 -agonist use and the variability of peak expiratory flow, a correlate of bronchial hyperresponsiveness and the severity of asthma. Serum cortisol concentrations were significantly reduced in the group given high-dose budesonide (from a mean [\pm SE] of 18.4 ± 2.4 μg per deciliter to 15.9 ± 2.1 μg per deciliter, $P=0.02$) but were unchanged in the other group. The median serum theophylline concentration was 8.7 μg per milliliter (therapeutic range, 10 to 20) among those who received theophylline. Both treatments were well tolerated.

Conclusions For patients with moderate asthma and persistent symptoms, low-dose inhaled budesonide with theophylline and high-dose inhaled budesonide produced similar benefits. Effects were achieved at theophylline concentrations below the recommended therapeutic range. The addition of low-dose theophylline to inhaled glucocorticoid may be preferable to and cheaper than increasing the dose of inhaled glucocorticoid. (N Engl J Med 1997; 337:1412-8.)

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INHALED glucocorticoids have become the mainstay of therapy in asthma, with dose titration until control is achieved.¹ Although it is effective, the long-term consequences of such treatment are not known.² Furthermore, because of the prevalence of asthma and the expense of treatment, this condition places a considerable burden on health care systems.³

Theophylline has been used in asthma for over 50 years and is prescribed throughout the world, but its popularity has declined because it is not classified as an antiinflammatory agent and it is a less effective bronchodilator than β_2 -agonists.⁴ Furthermore, there is concern about the side effects of theophylline, such as nausea, vomiting, and cardiac arrhythmias. Recent studies have shown that theophylline has immunomodulatory effects.⁵⁻⁸ The drug inhibits late responses to allergen challenge,^{9,10} with inhibition of allergen-induced migration of eosinophils into the lung,⁷ and it may inhibit trafficking of T lymphocytes into the airway.⁶ In vitro studies also show immunomodulatory effects, including decreased release of mediators from inflammatory cells.¹¹⁻¹³

Short-term studies have shown that theophylline improves lung function when added to a regimen of oral or inhaled glucocorticoid for asthma.¹⁴⁻¹⁶ Current guidelines recommend increasing the dose of inhaled glucocorticoid in patients whose asthma is not controlled by lower doses (400 to 800 μg of budesonide).^{17,18} However, studies have shown that adding long-acting β_2 -agonists to the regimen rather than increasing the dose of glucocorticoid may be more beneficial.^{19,20} We designed a study to compare the effect of adding low-dose theophylline to a regimen of inhaled glucocorticoid with that of increasing the dose of glucocorticoid in people with asthma who remain symptomatic while taking 800 to 1000 μg of budesonide daily.

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METHODS

Patients

The study was conducted between October 1994 and May 1996 and was approved by the ethics committees at both study centers. All patients gave written informed consent. All patients had the cardinal features of asthma — paroxysmal wheeze, cough, and breathlessness — and fulfilled the American Thoracic Society criteria for asthma.²¹ Despite treatment with inhaled budesonide at a daily dose of 800 to 1000 μg (or equivalent doses of beclomethasone dipropionate or fluticasone propionate), patients continued to have cough, wheeze, or breathlessness during the day or at night. All patients had a forced expiratory volume in one second (FEV_1) that was more than 50 percent of the predicted value and whose abnormalities were reversible with albuterol (defined as an increase in the absolute FEV_1 of more than 15 percent or as an increase in the predicted FEV_1 of at least 9 percent 15 or 30 minutes after the administration of 200 μg of albuterol).

No patient had received oral glucocorticoids for three weeks before the run-in period, nor had anyone taken more than three courses of glucocorticoids within the preceding six months. Patients who had had an exacerbation of asthma or who had taken theophylline or any other treatment for asthma within three weeks of the run-in period were ineligible. A history of serious diseases or other lung conditions also precluded entry into the study.

Study Protocol

A screening visit was followed by a two-week run-in period, randomization at base line, and a three-month treatment period. The patients kept diary cards throughout the study. The patients returned every three weeks during the treatment period and then one week after treatment ended for a follow-up visit.

Screening Visit

At screening, if no short-acting β_2 -agonists had been used within six hours, base-line lung function — peak expiratory flow (PEF), FEV_1 , and forced vital capacity (FVC) — and the reversibility of abnormalities in FEV_1 were recorded. FEV_1 and FVC were measured with a dry wedge spirometer (Vitalograph, Buckingham, United Kingdom). PEF was measured with a Mini-Wright peak-flow meter (Clement Clarke, Harlow, Essex, United Kingdom). The highest of three PEF measurements and the best FEV_1 and FVC from any of three efforts were recorded.

The patients were then prescribed a budesonide inhaler and a spacer device and instructed to take 400 μg of budesonide twice daily during the run-in period. Patients were also given an albuterol inhaler, with instructions to use it as required.

The patients were issued a diary card and asked to make twice-daily entries of three PEF measurements, albuterol usage, and the severity of symptoms, if any. A 4-point scale was used to assess the severity of cough, wheeze, and breathlessness, with a score of 0 indicating the absence of any symptoms; a score of 1 mild symptoms; a score of 2 moderate symptoms; and a score of 3 severe symptoms; the maximal score was 9. To undergo randomization, during the final week of the run-in period patients had to have either a score of 4 or more than a 10 percent variation in day-to-day PEF, calculated as $(\text{highest daily PEF} - \text{lowest daily PEF}) \div \text{highest daily PEF} \times 100$. Symptom scores and albuterol use recorded in the morning were for events from the preceding night, and information recorded in the evening referred to events that occurred during the day.

Base-Line Measurements

For the base-line measurements, lung function was again assessed and the reversibility of abnormalities in FEV_1 established (if not previously determined). The mean morning PEF from the last week of the run-in period served as the base-line value. Patients were randomly assigned to receive either 400 μg of budesonide plus either 250 mg of theophylline (if they weighed less than 80 kg) or 375 mg of theophylline (if they weighed 80 kg or more) or 800 μg of budesonide plus placebo. All doses were given twice daily. The appearance of placebo was identical to that of theophylline. Randomization was stratified to ensure that the severity of symptoms was equal in the two groups. There were two strata of severity, defined according to PEF: patients with a PEF that was less than 75 percent of the predicted value and those with a higher PEF. Blood samples were taken to determine base-line theophylline levels and morning serum cortisol concentrations.

Randomization was stratified to ensure that the severity of symptoms was equal in the two groups. There were two strata of severity, defined according to PEF: patients with a PEF that was less than 75 percent of the predicted value and those with a higher PEF. Blood samples were taken to determine base-line theophylline levels and morning serum cortisol concentrations.

Study Visits

At each visit during treatment and at follow-up, lung function was assessed and exacerbations of asthma were recorded as mild (two consecutive days with any of the following: decrease in morning PEF by more than 20 percent of base line, nocturnal symptoms, or the need for more than four puffs of albuterol) or severe (decrease in morning PEF by more than 30 percent on two consecutive days). Lung function was measured at least six hours after β -agonists were last given. Blood was taken for the measurement of theophylline levels at each visit, and a second sample was also obtained in the morning (8 a.m.) at 12 weeks to measure serum cortisol.

Drugs and Laboratory Analyses

Patients were prescribed theophylline (Euphylong, Byk Gulden, Konstanz, Germany) or matched placebo. This formulation of theophylline has established, reproducible sustained-release pharmacokinetic properties.²² Budesonide was supplied by Astra Draco, Lund, Sweden. The inhalers used were identical irrespective of treatment group.

Serum theophylline levels were determined with a particle-enhanced turbidimetric inhibition immunoassay (Synchron CX Systems, Beckman Instruments, High Wycombe, United Kingdom). Cortisol was measured with a fluorescence polarization immunoassay (Abbott, Maidenhead, United Kingdom).

Statistical Analysis

We investigated the differences in benefit between the test treatment (low-dose inhaled budesonide plus theophylline) and the reference treatment (high-dose inhaled budesonide). Outcome variables were obtained either from the diary cards (morning and evening PEF, severity of symptoms, albuterol use, and variability in PEF) or from clinic data (lung function and serum cortisol concentrations). The sample size was calculated for the primary end point, morning PEF; a sample of 31 patients per group was sufficient to detect with a power of 80 percent a 10 percent difference in improvement over base-line values, with a coefficient of variation of 15 percent.

Measurements of PEF, FEV_1 , and FVC, changes in predicted FEV_1 and FVC, and PEF measurements from the daily diary cards are presented as means \pm SE. Pretreatment and post-treatment data were compared within groups by Student's paired t-test (two-sided). Bonferroni's correction was used to account for the multiple comparisons.

For comparison of global effects of treatments, improvements in lung-function variables were averaged for the four time points during the treatment periods and then subjected to analysis of variance after logarithmic transformation. We calculated time-point-specific two-sided confidence intervals for the ratios of test-treatment effects to reference-treatment effects after adjustment for base-line values (with Bonferroni's correction for multiple comparisons), using the residual variance from a repeated-measures analysis of variance.²³

Symptom scores, the number of puffs of albuterol, and the variability in PEF were expressed as medians with ranges. Serum cortisol concentrations were expressed as means \pm SE. All these data were analyzed within groups by Wilcoxon's signed-rank test and

between groups by the Mann-Whitney U test. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Seventy-six patients were screened. Ten did not meet the inclusion criteria: two had exacerbations of asthma during the run-in period, one did not attend the follow-up visits, another declined to enter the treatment phase, and in six patients the abnormalities in FEV₁ were not reversible with albuterol. Sixty-six patients underwent randomization, and all but 4 completed the study, so that there were 31 patients in each group. Three of the patients who did not complete the study did not attend the clinic, and the other was excluded after undergoing randomization for investigation of anemia. There are no data on these patients.

The mean (\pm SE) age was 38.8 ± 1.8 years (range, 18 to 67). The demographic features and severity of asthma were similar in the two groups, as were the mean daily doses of inhaled glucocorticoid and the number of courses of oral glucocorticoid given in the six months preceding the run-in period (Table 1).

All patients complied with treatment with inhaled budesonide, and there were no instances of non-compliance among the patients who received theophylline. In this group the median serum theophylline concentration was $8.7 \mu\text{g}$ per milliliter (range, 2.5 to 17.1). Both treatments were well tolerated. Nine patients who received low-dose inhaled budesonide plus theophylline reported adverse events that may have been drug related (gastrointestinal upset in five patients, palpitations in two, sore throat in one, and headache in one), as did seven patients in the group given high-dose inhaled budesonide (sore throat in three, gastrointestinal upset in two, rosacea in one, and palpitations in one).

Lung Function at Clinic Visits

Both treatments resulted in improvements in lung function that were sustained throughout the study (Fig. 1 and 2). In the group given high-dose budesonide the FEV₁ values increased from 2.50 ± 0.14 liters at base line to a peak of 2.62 ± 0.15 liters at week 9 ($P=0.37$) and 2.61 ± 0.14 liters at week 12 ($P=0.12$). FVC increased from 3.49 ± 0.15 liters to a peak value of 3.73 ± 0.14 liters at week 9 ($P=0.16$) and a final value of 3.67 ± 0.16 liters ($P=0.27$). PEF increased at all time points from a base-line value of 411 ± 16 liters per minute, reaching a peak of 436 ± 18 liters per minute at week 12 ($P=0.02$) (Fig. 2).

In the group given low-dose budesonide plus theophylline, the FEV₁ increased from 2.48 ± 0.18 liters at base line to a peak of 2.76 ± 0.18 liters at week 9 ($P=0.002$) and a final value of 2.69 ± 0.16

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

CHARACTERISTIC	HIGH-DOSE BUDESONIDE PLUS PLACEBO (N=31)	LOW-DOSE BUDESONIDE PLUS THEOPHYLLINE (N=31)
Male sex (no. of patients)	10	15
Age (yr)		
Mean \pm SE	39.5 ± 2.6	38.1 ± 2.5
Range	18–66	18–67
Morning PEF (liters/min)†		
Mean \pm SE	383 ± 16	397 ± 19
Range	194–500	207–624
FEV ₁ (liters)		
Mean \pm SE	2.50 ± 0.14	2.48 ± 0.18
Range	1.21–3.96	1.34–4.75
FEV ₁ (% of predicted value)		
Mean \pm SE	78 ± 4	72 ± 4
Range	39–115	35–116
Response of FEV ₁ to albuterol inhalation (% change from base line)‡		
Mean \pm SE	21 ± 2	22 ± 2
Range	9–44	8–52
Daily dose of inhaled budesonide (μg)§		
Mean \pm SE	702 ± 40	671 ± 59
Range	133–1000	67–1000
Serum cortisol ($\mu\text{g}/\text{dl}$)¶		
Mean \pm SE	18 ± 2.4	13.9 ± 1.2
Range	5–47	6–31
PEF variability (%)		
Mean \pm SE	8.4 ± 1.0	9.7 ± 1.0
Range	0.55–28.5	1.54–24.0

*PEF denotes peak expiratory flow, and FEV₁ forced expiratory volume in one second.

†Values are the means of diary-card data obtained during the final seven days of the run-in period.

‡The mean percent change in FEV₁ after the inhalation of 200 μg of albuterol was measured. Patients with an absolute increase in FEV₁ of more than 15 percent or with an increase of at least 9 percent in the predicted FEV₁ 15 or 30 minutes after the administration of albuterol were eligible for the study.

§Values are the mean daily doses of inhaled budesonide (or equivalent) during the six months before the run-in period. The values were established from hospital records and were based on the assumption that 1 mg of budesonide is equipotent to 1 mg of beclomethasone and 500 μg of fluticasone.

¶ $P=0.69$ for the difference between groups. To convert values to nanomoles per liter, multiply by 27.59.

||The mean daily variability in peak flow was calculated during the final seven days of the run-in period.

liters ($P=0.009$). The FVC values increased at all time points, rising from 3.52 ± 0.19 liters at base line to a peak value of 3.84 ± 0.2 liters at week 6 ($P=0.001$) and a final value of 3.78 ± 0.18 liters ($P=0.002$). PEF in the group given low-dose inhaled budesonide plus theophylline increased from 430 ± 21 liters per minute at base line to a peak of 464 ± 20 liters per minute at week 9 ($P=0.004$) and a final value of 453 ± 19 liters per minute ($P=0.009$) (Fig. 2).

Analyses of overall treatment effects of the two treatments showed similar improvements in PEF ($P=0.16$). Low-dose budesonide plus theophylline

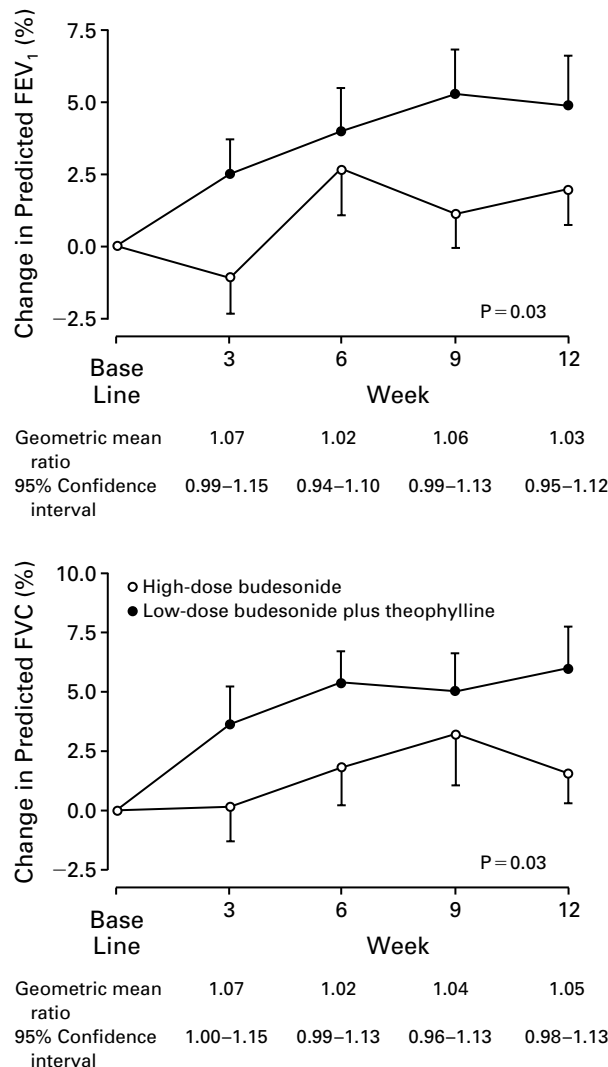


Figure 1. Mean (\pm SE) Changes in Lung Function in 31 Patients Treated with High-Dose Budesonide and 31 Patients Given Low-Dose Budesonide plus Theophylline.

Forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were measured at clinic visits. Two-sided P values, obtained by analysis of variance, are for the comparison of overall treatment effects with respect to FEV₁ and FVC. The values below the figure are time-point-specific geometric means for the ratios of test-treatment effects to reference-treatment effects (adjusted for base-line values) and two-sided 95 percent confidence intervals, with Bonferroni's correction for multiple comparisons.

was superior to high-dose budesonide in terms of both FEV₁ (P=0.03) and FVC (P=0.03) (Fig. 1).

Home Recordings of PEF

There were sustained increases in mean PEF recorded in the morning in both treatment groups. However, these changes did not reach significance at any time point in the group given high-dose budesonide.

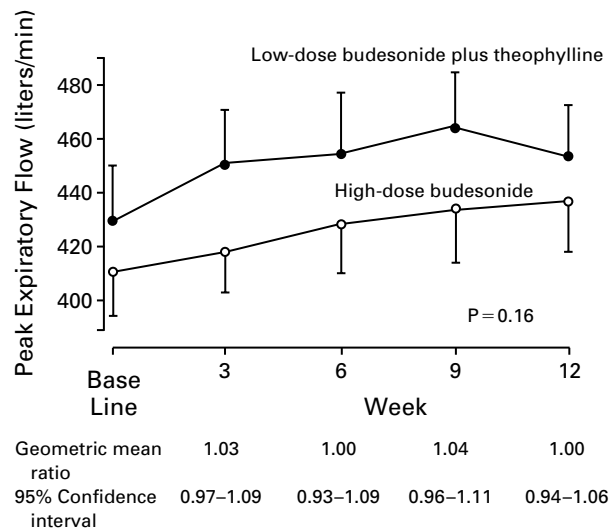


Figure 2. Mean (\pm SE) Peak Expiratory Flow (PEF) in 31 Patients Treated with High-Dose Budesonide and 31 Patients Given Low-Dose Budesonide plus Theophylline.

Measurements were made at clinic visits. The two-sided P value, obtained by analysis of variance, is for the comparison of overall treatment effects with respect to PEF. The values below the figure are time-point-specific geometric means for the ratios of test-treatment effects to reference-treatment effects (adjusted for base-line values) and two-sided 95 percent confidence intervals, with Bonferroni's correction for multiple comparisons.

onide. In the group given low-dose budesonide plus theophylline the improvements were only significant at weeks 3 and 6. Analyses of overall treatment effects for PEF measured by the patients showed no significant difference between treatments (P=0.60) (Table 2).

During the study the variability in PEF improved significantly in both groups (Table 2). High-dose budesonide led to a median reduction of 8.9 percent in PEF variability (P=0.03), and low-dose budesonide plus theophylline led to a reduction of 28.6 percent (P=0.004). These changes were not significantly different between the two groups (P=0.23).

Use of Short-Acting β_2 -Agonists and Symptom Scores

The severity of symptoms decreased in both groups. Patients given high-dose budesonide reported reductions in the severity of symptoms during the day (P=0.002) and at night (P=0.05), and patients given low-dose budesonide plus theophylline reported reduced symptoms at night (P=0.08) (Fig. 3). There were no significant differences between the groups in these variables (P=0.57 for daytime β -agonist use; P=0.97 for nighttime β -agonist use; P=0.26 for severity of daytime symptoms; and P=0.59 for severity of nighttime symptoms).

TABLE 2. CHANGES IN PEAK EXPIRATORY FLOW, AS MEASURED BY THE PATIENTS.*

VARIABLE	BASE LINE	WEEK			
		3	6	9	12
High-dose budesonide plus placebo					
Morning PEF	383±16	399±15	401±17	398±17	405±17
P value		+0.07	0.04	0.08	0.03
Evening PEF	399±15	410±16	414±18	414±18	412±18
Variability in PEF (%) [†]	—	+1.4	-7.3	-2.3	-8.9 [‡]
Low-dose budesonide plus theophylline					
Morning PEF	397±19	410±18	420±19	417±21	411±19
P value		0.005	0.002	0.14	0.02
Evening PEF	419±18	425±17	432±19	438±20	430±18
Variability in PEF (%) [†]	—	-24.3	-15.1	-20.1	-28.6 [‡]
Geometric mean ratio (95% CI) [§]	—	0.99 (0.92-1.07)	1.01 (0.95-1.07)	1.00 (0.94-1.06)	0.99 (0.93-1.08)

*Plus-minus values are means ±SE. PEF denotes peak expiratory flow, and CI confidence interval. In each case values are the means for the week preceding the clinic visit. Two-sided P values are for the comparison with base-line values within treatment groups.

[†]Values are the median change in PEF variability from base line.

[‡]The change at week 12, as compared with the base-line value, was significant in the group given low-dose budesonide plus theophylline (two-sided $P=0.004$) and in the group given high-dose budesonide ($P=0.03$).

[§]Geometric means, with two-sided 95 percent confidence intervals (with Bonferroni's correction for multiple comparisons), are the ratios of test-treatment effects to reference-treatment effects.

The use of short-acting β_2 -agonists was reduced during the day in both groups ($P<0.001$ for the group given low-dose budesonide plus theophylline and $P=0.008$ for the group given high-dose budesonide) and at night in the group given low-dose budesonide plus theophylline ($P=0.05$) (Fig. 3).

Exacerbations of Asthma

There were a median of 3 (range, 0 to 11) mild exacerbations of asthma in the group given high-dose budesonide and 2 (range, 0 to 13) in the group given low-dose budesonide plus theophylline. There were three severe exacerbations during the study (two in the group given high-dose budesonide and one in the other group), and all were treated with oral glucocorticoids.

Serum Cortisol Levels

The morning serum cortisol values at base line were 18.4 ± 2.4 μg per deciliter (509 ± 67 nmol per liter) in the group given high-dose budesonide and 13.9 ± 1.2 μg per deciliter (386 ± 35 nmol per liter) in the group given low-dose budesonide plus theophylline. After three months of treatment there was a reduction in serum cortisol concentrations to 15.9 ± 2.1 μg per deciliter (439 ± 59 nmol per liter) in the group given high-dose budesonide ($P=0.02$), but not in the group given low-dose budesonide plus theophylline (final value, 13.9 ± 1.3 μg per deciliter [384 ± 35 nmol per liter]; $P=0.40$). Although suppression occurred only in the group given high-dose budesonide, this did not result in a significant difference between the two groups ($P=0.09$).

DISCUSSION

Our study shows that the combination of low-dose inhaled budesonide plus theophylline and conventional treatment with high-dose inhaled budesonide produced similar results in patients whose asthma was not controlled by 800 μg of budesonide daily. In terms of lung function, FEV₁ and FVC significantly improved among those given theophylline. We believe that this effect is real, since the changes were sustained and are in agreement with those seen in other studies examining inhaled glucocorticoids and theophylline.^{16,24} These effects occurred at a median concentration below the therapeutic range. Treatment with theophylline at concentrations below 10 μg per milliliter offers benefits while reducing the risk of side effects. The superiority of the treatment with added theophylline in terms of FVC is noteworthy. Oral theophylline may be more likely to reach the small airways than inhaled glucocorticoids, resulting in greater increases in FVC.

Our results are compatible with those of studies that examined the effects of adding salmeterol to inhaled glucocorticoid.^{19,20} These studies reported even greater increases in PEF than in our patients. However, salmeterol did not decrease the variability in PEF, as did theophylline plus low-dose budesonide in our study. Differences in study design and populations prohibit further comparisons. In particular, neither this study nor those involving salmeterol examined inflammation. Bronchodilation remains the most likely explanation for benefits seen in both studies of salmeterol.^{19,20}

The question remains whether theophylline exerts

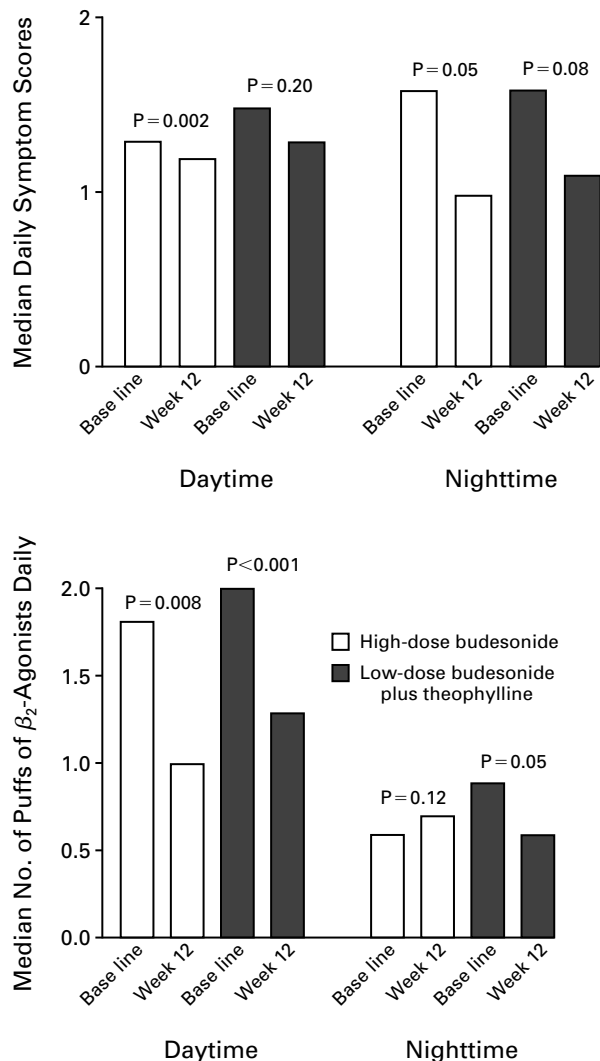


Figure 3. Recorded Need for Additional Medications and Severity of Symptoms.

The data were obtained from patients' daily diary cards. A score of 0 indicated the absence of any cough, wheeze, or breathlessness; a score of 1, mild symptoms; a score of 2, moderate symptoms; and a score of 3, severe symptoms. Scores were averaged for the last week of the run-in period (base line) and the final week of the treatment period (week 12). Two-sided P values are for differences between base line and week 12.

a nonbronchodilator effect. Without data on inflammation, it is not possible to conclude whether the drug has immunomodulatory effects. Nonetheless, immunomodulation could account for some of the effects seen. The delayed but sustained improvements in both FEV₁ and FVC were similar in our patients who were given high-dose budesonide and in the patients given high-dose glucocorticoid in the salmeterol studies.^{19,20} Salmeterol-induced bronchodilation was characterized by rapid improvements in lung function,^{19,20} an effect not observed in our

study. In addition, in our study, the extent of the reduction in the variability of PEF differed between groups. Variability of PEF is a correlate of bronchial hyperresponsiveness and the severity of asthma.²⁵ Bronchodilation alone would not explain this difference in diurnal airway function.

There was a significant reduction in endogenous cortisol in the group given high-dose budesonide. The clinical relevance is uncertain,² although until the safety of this regimen is established it may be preferable to use glucocorticoid-sparing regimens instead.

The approximate monthly cost of daily treatment with theophylline and 800 μ g of budesonide is \$60, as compared with \$100 for 1600 μ g of budesonide daily and \$155 for the combination of 800 μ g of budesonide and 100 μ g of salmeterol daily. Thus, the combination of theophylline with low-dose budesonide is substantially less expensive.³

Our results show that the addition of theophylline was beneficial in patients whose asthma was not controlled by 800 to 1000 μ g of inhaled glucocorticoid a day and supports its use as a glucocorticoid-sparing agent. Effects were achievable at lower doses of theophylline than previously used, thus minimizing side effects. Although inhaled glucocorticoids remain central to the treatment of asthma, combining theophylline and inhaled glucocorticoids may be a more attractive and cheaper option than using higher doses of glucocorticoids.

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