

Aerosol beclomethasone dipropionate spray compared with theophylline as primary treatment for chronic mild-to-moderate asthma

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Allergy, Asthma and Immunology Beclomethasone Dipropionate-Theophylline
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Background: Inhaled corticosteroids and oral theophylline are effective treatments for moderate asthma.

Objective: We sought to compare the benefits and adverse reactions of theophylline and aerosol beclomethasone spray.

Methods: A multicenter, double-blind, double-placebo, randomized, controlled trial of 1-year duration was performed. Seven hundred forty-seven patients with asthma received either beclomethasone dipropionate aerosol spray (84 µg four times per day) or sustained-release theophylline twice per day in doses adjusted for optimum control of the disease. The main outcome measures were daily diary of symptoms and peak flow rates (recorded on a mark-sense computer-readable form); supplemental bronchodilator use; doctor's office or hospital visits and absence from work or school; spirometry; methacholine testing; adverse experiences; and cortisol blood measurements.

Results: Both treatment strategies reduced symptoms promptly and achieved low absenteeism from work or school and low rates of emergency treatment for asthma. Both maintained nearly normal pulmonary function. Beclomethasone was statistically significantly more effective in reducing symptoms, supplemental bronchodilator and systemic glucocorticoid doses, bronchial hyperresponsiveness, and eosinophilia. However, the magnitude of these differences was small. Theophylline caused more headache, nervousness, insomnia, and gastrointestinal distress, and more patients discontinued treatment because of side effects. Beclomethasone caused more oropharyngeal candidiasis and hoarseness and reduced morning plasma cortisol levels before and after cosyntropin. It reduced the rate of growth in children. No new cataracts or glaucoma developed.

Conclusion: Theophylline effectively controlled symptoms at lower than the customarily recommended blood level. The risk/benefit profiles of these agents suggest that inhaled corticosteroids may be the preferred agent for most adult patients and for some children. (*J Allergy Clin Immunol* 1998;101:14-23.)

Key words: Asthma, beclomethasone, theophylline

Abbreviation used

PEFR: Peak expiratory flow rate

The traditional concept of asthma as "bronchospasm" or "hyperreactive airway syndrome" has changed to the contemporary concept of asthma as chronic eosinophilic airway inflammation. This inflammation, originally described in autopsy specimens, is present in biopsy specimens from subjects with mild cases of asthma and can be briefly described as "desquamating eosinophilic bronchitis."¹⁻³ The Expert Panel Report II⁴ recommends regular antiinflammatory treatment with cromolyn, nedocromil, or an aerosol corticosteroid preparation for all patients who require more than occasional bronchodilator inhalation to control the disease. Theophylline is considered a second-line agent in the treatment of asthmatic subjects with moderate or severe disease.⁴ In part this recommendation is based on the report of Dutoit et al.⁵ that aerosol corticosteroid treatment increased the dose of methacholine required to induce a 20% fall in FEV₁ considerably more than theophylline did. Many physicians in the United States and several European countries have, however, continued to consider theophylline to be a primary medication to control mild-to-moderate chronic asthma.

Prolonged systemic administration of corticosteroids can cause many serious adverse effects that can be reduced by aerosol administration.⁶ The most frequently observed adverse effects of aerosolized corticosteroids have been oropharyngeal candidiasis and hoarseness.⁷ The importance of a dose-dependent systemic effect is controversial.⁶

The overall objective was to compare the magnitude of the advantages and disadvantages of aerosolized beclomethasone with theophylline for long-term, primary treatment of patients with mild-to-moderate chronic asthma that was inadequately controlled by bronchodilators and a reasonable attempt to avoid exposure to clinically significant allergens and irritants.

*Members of the study group are listed in the appendix.

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TABLE I. Reasons for exclusion from the study

- Cigarettes, cigars, pipe, or marijuana regularly smoked in the past 6 months or formerly smoked cigarettes for more than five pack-years (average packs [20 cigarettes/pack] per day times years smoked was >five)
- Acute respiratory infection within 3 weeks
- Systemic glucocorticoid treatment within the previous month or for more than 30 days in the previous two years
- Theophylline and aerosol glucocorticoid treatment together for more than 1 month in the previous year
- Regular aerosol cromolyn treatment within the previous 60 days
- Topical nasal glucocorticoid treatment in the past 30 days
- No maintenance dose with immunotherapy
- Serious adverse reactions to theophylline or glucocorticoids
- Other illnesses that would be a contraindication to theophylline or glucocorticoid treatment
- Attention deficit disorder, behavioral disorder, legal or mental incapacity, mental retardation, a history of alcohol or drug abuse, or other psychologic or emotional disorders that had required treatment
- History of any other illness or other required medications that could increase the risk of adverse reaction to the study drugs
- Pregnancy, lactation, or not using a reliable method of birth control.

METHODS

Study design

This was a randomized, double-blind, double-placebo study performed in 30 centers. The study subjects included both children and adults (6 to 65 years of age) with asthma who experienced dyspnea, cough, and wheezing and who required frequent bronchodilator treatment despite avoidance of allergens. These subjects were considered by their physicians to be candidates for continuous treatment. Within the month before randomization, patients were required to have an FEV₁ greater than 50% of predicted value before bronchodilator use and to demonstrate reversibility of airflow obstruction by at least 15%. Exclusion criteria are listed in Table I. The protocol was approved by the Institutional Review Board at each of the 30 study sites, and each patient (or the parent or guardian) signed a written consent form.

A screening phase to ensure that patients met entry criteria was followed by a prerandomization observation period of 1 month at the beginning of which patients previously receiving either theophylline or aerosol glucocorticoid treatment discontinued use of the drug. If the increase in symptoms became unacceptable to the patient or the investigator, if the FEV₁ decreased to less than 50% of predicted value before bronchodilator use, or if the FEV₁ failed to improve to values similar to those recorded during the screening phase after bronchodilator use, the observation period was terminated at the end of 2 or more weeks and the patient started randomized therapy. Patients who could not complete 2 weeks of observation were not randomly assigned. Randomization to either theophylline or beclomethasone dipropionate was stratified by clinical center, previous use of study drugs (theophylline, beclomethasone dipropionate, or other aerosolized glucocorticoid), and two age strata (6 to 16 years and 17 to 65 years).

Metered-dose inhalers delivering 42 mg per activation of beclomethasone dipropionate and placebo metered-dose inhalers that did not contain beclomethasone dipropionate (Allen &

TABLE II. Demographics of study patients

	Beclomethasone group (N = 384)	Theophylline group (N = 363)	Total (N = 747)
Age 6-17 yr			
F	45	28	73
M	57	65	122
Age 18-65 yr			
F	157	153	310
M	125	117	242
Race			
Asian	3	2	5
Black	29	20	49
White	343	332	675
Hispanic	9	9	18
Exposure to study drugs within the month before screening			
Neither beclomethasone nor theophylline	194	190	384
Theophylline only	175	160	335
Beclomethasone only	15	13	28

*Entries are numbers of patients.

TABLE III. Study completion status

Completion status	Beclomethasone group (N = 384)	Theophylline group (N = 363)	p Value
Completed	77.6	73.3	NS
Dropped because of:			
Noncompliance with study drug	5.0	5.8	NS
Adverse effect with study drug	2.9	6.3	0.023
Lack of benefit with study drug	4.4	4.1	NS
Subtotal	10.9	14.9	NS
Medical condition other than asthma	3.9	3.9	NS
Moved from area	1.0	1.7	NS
Administrative reasons	8.1	7.5	NS

Entries are percentages of patients. The *p* values are the two-tailed values from the 1 df chi-square test comparing each completion status separately in the two groups. Some patients enter more than one row. NS, Not significant.

Hanburys, Research Triangle Park, N.C.) were used in this study. We also used sustained-release theophylline capsules containing 100 and 300 mg of theophylline or matching placebo capsule. The active theophylline preparation was reencapsulated Slo Bid (Rorer Consumer Pharmaceuticals, Fort Washington, Pa.). The pharmacokinetics of the reencapsulated theophylline were determined to be the same as those of the original product.

The dosage of either sustained-release theophylline or matching placebo capsules was adjusted by a blinded study investigator to establish and maintain optimum control of asthma symptoms with minimum side effects. Theophylline

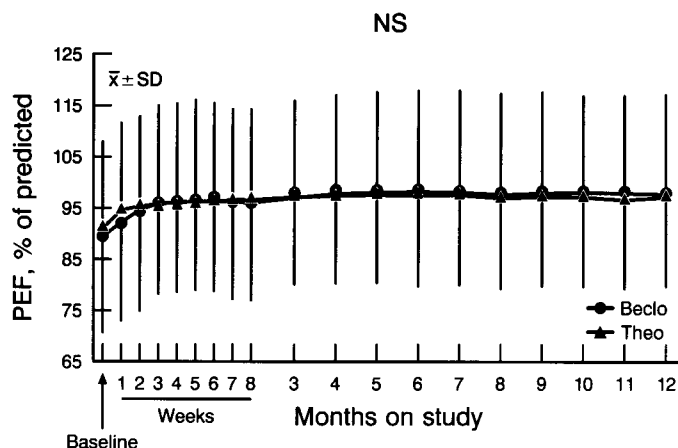


FIG. 1. Effect of beclomethasone and theophylline on daily peak flow rates. Each data point represents mean of daily morning and evening peak flow rates averaged over indicated interval. Separate analysis of morning, evening, and evening-morning difference yielded similar results. PEF, Peak flow rate.

blood levels were used as a secondary guide to dosing. To provide this guidance and to protect the patients from theophylline overdose, an unblinded investigator at each site received the report of the theophylline blood levels and directed the blinded investigator with a schedule of predetermined messages. The unblinded investigator interpreted the theophylline blood levels using a steady-state theophylline blood level of 8 to 15 $\mu\text{g/ml}$ at approximately 12 hours after a dose as a target. If the blood level was over 20 mg/L , the unblinded investigator directed that the dose be reduced. Other messages advising, but not requiring, a change of dose were sent appropriate to the other blood levels. The blinded investigator was free to respond to these suggestions or maintain the previous theophylline dose if the asthma was adequately controlled and side effects did not indicate otherwise. To maintain the blinded status of the study, a predetermined set of similar messages was sent for patients randomly assigned to receive placebo theophylline capsules and active beclomethasone dipropionate. In addition to the above capsules, all patients were instructed to inhale two puffs of either beclomethasone dipropionate aerosol spray (42 $\mu\text{g/puff}$) or matching placebo aerosol spray from a metered-dose inhaler without a spacer device four times per day in accordance with the inhalation instructions specified in the package insert. This dose was kept constant throughout the study for all subjects. If needed, symptoms were further controlled with an oral or aerosol β -adrenergic agonist, usually albuterol, or by short courses of oral or injected glucocorticoids, usually oral prednisone. Systemic glucocorticoid treatment was limited to 10 days in any 90-day period. Cromolyn or nedocromil was not permitted.

Patients returned for examinations at weeks 1, 2, 3, 4, 6, 8, 12, 24, and 36 and once during weeks 48 to 52. Spirometry was performed with standardized equipment and procedures recommended by the American Thoracic Society.⁸ Normal values for FEV_1 were calculated by the equations of Crapo et al.⁹ for adults and by the equation of Polgar and Promadhat¹⁰ for children. Normal values for peak expiratory flow rates (PEFRs) were those of Knudson et al.¹¹ and Hsu et al.¹² Corrections in predicted values for blacks were made by multiplying predicted peak expiratory flow and FEV_1 values by 0.85. Methacholine responsiveness, determined by the method of Chai et al.¹³ and expressed as PD_{20} , was determined at baseline, at weeks 6 and

12, and at the final visit. Clinical laboratory tests, blood count, serum chemistries, cortisol measurements, and pregnancy tests were performed at a central laboratory (SciCor, Indianapolis, Ind.). Blood theophylline levels, electrocardiograms, and chest radiographs were obtained locally. Each patient had an ophthalmologic examination focused on development of posterior subcapsular cataracts or increased intraocular pressure at the beginning of the study, at 6 months, and at the end of the study. Adrenal function was assessed by a morning cortisol measurement and cortisol measurements 30 and 60 minutes after an injection of cosyntropin at baseline, 6 months, and the final visit.

Throughout the year each patient kept a diary on a scannable scoring sheet designed for direct computer entry by optical scanning. They recorded daily asthma symptoms in the morning and the evening. The symptoms scored were difficulty in breathing, cough, and wheezing. These were scored as none (0), trivial or doubtful (1), mild (present, little or no discomfort) (2), annoying (no marked discomfort) (3), moderately severe (with marked discomfort) (4), severe (interference with sleep or activities, not incapacitating) (5), or incapacitating (6). Other daily entries included PEFs in the morning and the evening, doses of study medications, numbers of puffs or tablets of albuterol (or equivalent medications), absence from work or school, and doctor's office or emergency department visits or hospitalizations for asthma. In all, 229,980 diary days were analyzed.

Case report forms recorded interim history, physical examinations, adverse experiences, emergency department visits and hospitalizations, changes in medication, results of the various tests, and physician assessments.

Statistical methods

All 747 patients who met the criteria for randomization were included for analysis of efficacy outcomes. An additional 24 patients, after being randomized and receiving study medications, were found not to have met all entry criteria. These additional patients were included only in the analysis of adverse patient-reported experiences.

To reduce the volume of information from the daily diaries to workable form, the information was summarized on two levels. For various selected study intervals (e.g., baseline, week 1), we

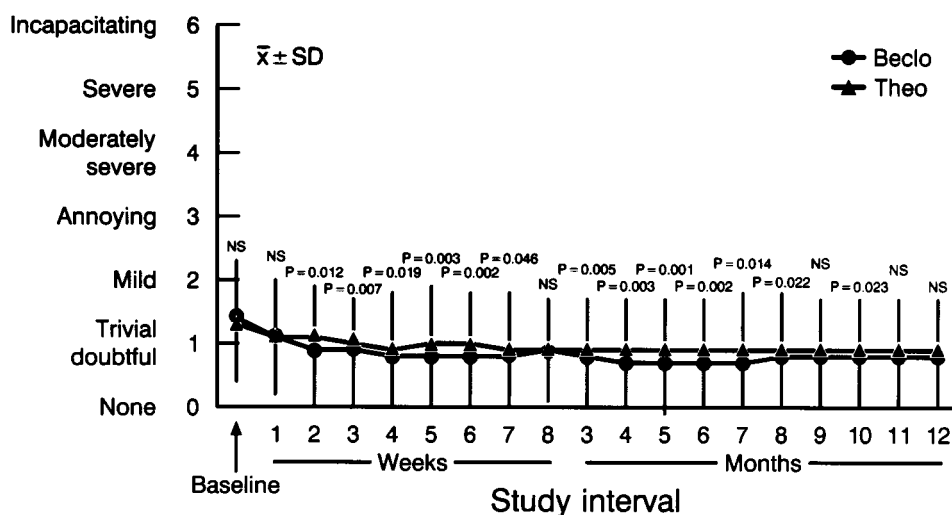


FIG. 2. Effect of beclomethasone and theophylline on daily symptoms scores. Each data point represents mean of scores recorded twice a day for each of three symptoms (cough, wheeze, and difficulty breathing) averaged over indicated interval.

first summarized the findings for each patient over the days in the interval (e.g., mean PEFR over month 1 of study). Second, the individual patient summaries were compared among those assigned the two study medications. Not all patients adhered to the prescribed schedule of visits and tests. Therefore for each outcome we considered the distribution of days between initiation of study medication use and test performance. A window of acceptable days was set without knowledge of random drug assignment. If the visit fell outside this window, the data were included in the analysis of the time period in which the visit actually took place. To assess changes over time of the study, patients' specific rates of change were computed using simple linear regression techniques. These rates of change were then summarized and compared in the two groups.

Statistical tests used included: Fisher's exact test, Mantel-Haenszel test,¹⁴ chi-square test of association, log-rank test for comparing time receiving study drug,¹⁵ rank sum tests, and linear regression analysis. Only two-tailed *p* values are reported with the conventional 0.05 level taken to reflect statistical significance.

RESULTS

Patient numbers, demographic characteristics, and previous experience with the study drugs are listed in Table II. Forty-five percent of all subjects had previously taken theophylline, 4% had previously taken beclomethasone, and 51% had not used either drug.

About 90% of the patients receiving beclomethasone recorded that they took 2 puffs of aerosol four times per day. The median dose of theophylline for adults was 600 mg/day after the first month. The median dose for children was 400 mg/day at 1 month and 600 mg/day after the eighth month. About a third of the patients had theophylline blood levels in the targeted 8 to 15 mg/ml range 12 hours after a dose, whereas 11% of the subjects receiving theophylline did not have a blood level over 4 mg/ml at any of the times tested during the study.

The study completion rate was 78% for subjects

receiving beclomethasone and 73% for those receiving theophylline. One half of the drop-outs occurred by week 17, and the remainder occurred between week 18 and the end of the study. Kaplan-Meier survival curves for time in study were not significantly different between groups as determined by a log-rank test (data not shown). Reasons for early termination are listed in Table III; the only category that was significantly different was that 6% of the patients withdrew because of adverse experiences with theophylline, compared with 3% with beclomethasone.

Efficacy

Contrary to the hypothesis that theophylline would act faster, both regimens improved peak flow rates and symptoms promptly (Figs. 1 and 2).

Outcomes in which beclomethasone dipropionate and theophylline were similar included the following. First, monthly mean evening PEFRs ranged from 97% to 100% of predicted value for both beclomethasone dipropionate and for theophylline, and morning values ranged from 92% to 96% and 94% to 96% of predicted normal for the two respective groups. The monthly median percentage change ($100 \times [\text{Evening} - \text{Morning}] / \text{Evening}$) ranged from 1.3% to 3.0% in the beclomethasone dipropionate group and 1.3% to 1.9% in the theophylline group. Only in the first month was there a slightly larger difference in the median percentage drop in the beclomethasone dipropionate-treated patients (3.0% vs 1.9%, $p = 0.01$).

Second, the prebronchodilator FEV₁ improved promptly over the course of study in both groups. In the beclomethasone dipropionate-treated patients, it rose from a baseline level of 71.1% to 82.6% at week 1. Over weeks 2, 3, 4, 8, 12, and 36, the mean values ranged from 81.7% to 83.5% of predicted value. In the theophylline

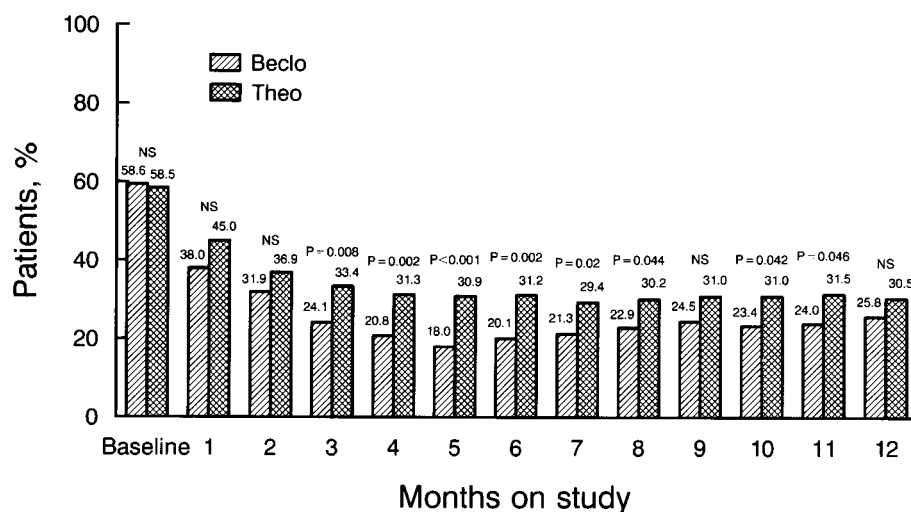


FIG. 3. Effect of beclomethasone and theophylline on occurrence of moderately severe or worse symptoms. Percent of subjects who recorded a score of 4 or more (moderately severe or worse) for any one of the symptoms (cough, wheeze, or difficulty breathing) on any day during indicated period.

group, the mean FEV₁ rose from 72.7% at baseline to 82.9% at week 1 and ranged subsequently from 81.5% to 83.9%. Postbronchodilator mean values for beclomethasone dipropionate ranged from 90.2% to 92.5%, and for theophylline they rose from 90.6% to 92.3% with no significant differences over time. The mean percent reversibility ($100 \times [\text{Postbronchodilator} - \text{Prebronchodilator}] / \text{Prebronchodilator}$) for beclomethasone dipropionate changed from 27.8% at baseline and ranged from 11.0% to 12.6% over subsequent visits. For theophylline, it was 27.2% at baseline and subsequently ranged from 11.1% to 13.3%.

Third, over the 12 months patients received the study drugs, the percentage of patients with one or more doctor's office visits, emergency department visits, or hospitalizations for asthma each month varied from 1.2% to 4.1% in the beclomethasone dipropionate group and 1.3% to 4.7% in the theophylline-treated group. Only 19.2% versus 19.8% of the subjects ever required such treatment, and only 1.6% versus 1.4% needed hospitalization for asthma at any time during the course of the study in the respective groups.

Fourth, during the study interval, 24% of patients receiving beclomethasone dipropionate and 23% of those receiving theophylline missed one or more days from work or school because of asthma. No outcomes favored theophylline.

Outcomes that favored beclomethasone dipropionate were as follows. First, beclomethasone dipropionate was better at keeping symptoms under control. Although mean total symptom scores declined from baseline and were low in both groups, they were lower in the beclomethasone-treated group (Fig. 2) ($p = 0.002$ at 6 months). Patients in the beclomethasone group reported fewer days during the month with symptoms they considered moderately severe or worse ($p = 0.002$ at 6 months) (Fig. 3).

Second, a higher proportion of patients in the beclomethasone dipropionate group had more days in which they did not use any supplemental bronchodilator medication ($p = 0.038$ at 6 months) (Fig. 4).

Third, the beclomethasone dipropionate group required less systemic glucocorticoid treatment. Over the course of the study, 20% of the beclomethasone dipropionate-treated group needed one or more courses of treatment compared with 29% of those receiving theophylline (rank sum test on number of courses, $p = 0.009$).

Fourth, beclomethasone dipropionate, in contrast to theophylline, produced a modest, though statistically significant, improvement in methacholine sensitivity. During the 12 months of the study, the PD₂₀ for methacholine in the theophylline group did not change. After 6 weeks of treatment with beclomethasone, the mean PD₂₀ increased by about one half of a doubling dilution. This increase in PD₂₀ was maintained at 12 months ($p < 0.05$ at 6 weeks and $p < 0.001$ at 1 year).

Fifth, at the completion of the year's observation, the physician's global assessment favored beclomethasone dipropionate ($p = 0.008$). Response was considered excellent in 33% of patients treated with beclomethasone and 26% of patients treated with theophylline. A good response occurred in 53% versus 51%, a fair response in 11% versus 20%, and a poor response in 3% versus 4%.

Sixth, at the end of the study, the peripheral blood eosinophil count (cells per milliliter) had declined in the group receiving beclomethasone from a mean $\pm$ SD of 369 ± 291 to 286 ± 213 , but it did not change in the group receiving theophylline (baseline, 371 ± 296 to 407 ± 309). The beclomethasone dipropionate-treated patients had a significantly smaller mean at the end of the study ($p < 0.001$), as well as a larger decrease from baseline ($p < 0.001$). Neither drug affected the number

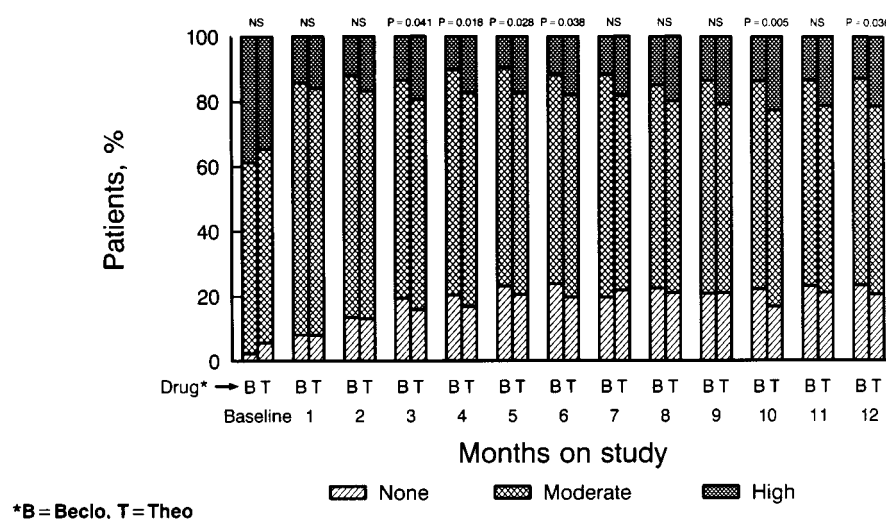


FIG. 4. Effects of beclomethasone and theophylline on frequency of use of supplemental bronchodilator tablets or aerosol spray. Supplemental bronchodilator medication use during a study interval was defined as follows: *none* = no supplemental bronchodilator medication used in interval; *moderate* = mean puffs of aerosol bronchodilator greater than 0 ranging up to and including 6 per day and/or oral bronchodilator use from 1% to 75% of days in interval; *high* = mean puffs of aerosol bronchodilator greater than 6 per day or oral bronchodilator use greater than 75% of days in interval.

of neutrophils or lymphocytes or the plasma glucose or potassium concentration.

Adverse experiences

There were no life-threatening adverse effects attributable to the study medications. One man in the beclomethasone group had a nonfatal myocardial infarct. One man committed suicide, and a teenaged girl took an overdose of the study medication but survived. Both of these psychiatric problems were in the theophylline group. There were no instances of seizures, gastrointestinal bleeding, or paroxysmal tachycardia. Because many of the adverse experiences described on the case report forms at study visits are common symptoms that have a variety of causes, the adverse experiences could not be ascribed to either study medication with certainty. We have therefore analyzed them in two ways: first, all experiences the patients reported, and second, only those experiences that the physicians considered possibly, probably, or almost certainly related to the study drugs. All reported adverse events were analyzed. Those that were different in the two study groups are listed in Table IV.

More patients taking theophylline had headaches, insomnia, tremor, nervousness, and dizziness presumably from its effect on the central nervous system and skeletal muscle. More of them also had gastric irritation, dyspepsia, nausea, and vomiting.

More patients taking beclomethasone dipropionate had oropharyngeal candidiasis, voice disturbance, hoarseness, and acute pharyngitis. Interestingly, the number of patients with one or more upper respiratory tract infections was similar (2.5% in the beclomethasone group and 2.9% in the theophylline group).

The means of the morning cortisol levels were similar in the two groups at the beginning of the study, but by 6 and 12 months, they were lower in the group treated with beclomethasone dipropionate both before and after cosyntropin injection (Fig. 5). Review of the individual case records disclosed no instance of a morning cortisol level below 5 mg/dl that could be attributed to the aerosol treatment. When observed, these low values were either at the baseline visit, in the theophylline-treated group, or during or shortly after a course of systemic glucocorticoid administration. Ophthalmologic examinations performed before and after the treatment period uncovered no instances of newly developed posterior subcapsular cataract or glaucoma attributable to aerosolized beclomethasone.

DISCUSSION

The aim of this investigation was to compare how well these two treatments control moderate asthma. The patient population had asthma severe enough that it was inadequately controlled by inhaled β -adrenergic agonists, but not so severe as to require more than occasional short courses of systemic glucocorticoids.

Both treatments were effective in achieving control and were accompanied by the anticipated effects. Both drugs acted promptly, although maximum reduction in symptoms was observed only after 2 to 4 weeks of therapy. In the first month, there was slightly less daily variation in PEFs in the theophylline-treated group. Both groups achieved acceptably low rates of absenteeism from work or school and episodes of emergency treatment or hospitalization and excellent PEFs and improvement in spirometry. Because the daily PEFs were greater than 90% of the predicted value for most

TABLE IV. Adverse experience profile

Symptoms	Overall % with finding			Study-drug related % with finding		
	Beclomethasone group (N = 394)	Theophylline group (N = 377)	p Value	Beclomethasone group (N = 394)	Theophylline group (N = 377)	p Value
Headache	42.4%	54.9%	0.001	25.9%	36.6%	0.001
CNS, not headache	6.6	20.7	<0.001	6.3	19.6	<0.001
Sleep disturbance	3.8	9.3	0.002	3.6	9.0	0.002
Abnormal involuntary movements	0.5	7.2	<0.001	0.5	6.4	<0.001
Nervousness	2.0	8.0	<0.001	2.0	8.0	<0.001
Gastric	22.6	37.9	<0.001	11.7	29.4	<0.001
Irritation/dyspepsia/nausea/vomiting						
Gastric irritation/dyspepsia	11.2	17.0	0.020	6.3	13.0	0.002
Dyspepsia/stomach disorder	9.4	11.7	NS	4.8	8.8	0.030
Nausea/vomiting	15.2	28.9	<0.001	6.3	21.2	<0.001
Dizziness/vertigo/light-headed	2.3	5.6	0.018	1.0	3.4	0.021
Disorders of the ear	0.8	3.2	0.015	0.0	0.5	NS
Oral candidiasis	8.9	2.4	<0.001	5.3	0.5	<0.001
Voice disturbances	5.3	1.1	0.001	4.6	0.3	<0.001
Acute pharyngitis	26.4	24.1	NS	8.4	4.0	0.012
Sore throat	26.1	23.6	NS	8.1	4.0	0.016
Kidney/urinary system	7.1	3.7	0.038	0.8	0.5	NS
Difficulty breathing	4.6	1.6	0.017	2.0	0.0	0.008*
Diseases of teeth and gums	2.8	0.5	0.015	0.0	0.0	NS

Entries are percentages of patients in the respective groups with one or more episodes of the finding over the entire course of the study. In the study-drug related column are findings considered by the physician to be possibly, probably, and almost certainly study-drug related. These judgments were made before randomization was revealed and without rigorous proof of drug causation.

NS, Not significant; CNS, central nervous system.

*Fisher's exact test. The remainder of the *p* values were obtained from the chi-square test of association for a 2 × 2 table.

patients, there was limited opportunity to detect significant improvements in this study. However, both theophylline and beclomethasone modestly improved peak flow rates. Mean prebronchodilator FEV₁ was only about 70% of predicted value and improved to greater than 80% of predicted value in both groups, a clinically significant difference.

Overall, asthma symptoms were mild throughout the study, on average ranging between trivial or doubtful (score = 1) and mild (score = 2). This would limit the opportunity to detect significant differences between treatment groups. There was a statistically significant advantage with beclomethasone in mean symptom scores, but this difference is probably not clinically significant.

When only troublesome symptoms are considered, the differences between treatment groups is more pronounced. About 30% of theophylline-treated subjects recorded moderately severe asthma symptoms (or worse) at least one day per month compared with 20% for beclomethasone-treated subjects. This difference is probably clinically significant. Furthermore, this superiority of beclomethasone in controlling moderately severe symptoms of asthma was achieved with less use of supplemental bronchodilator medication or systemic glucocorticoids. A study comparing inhaled fluticasone propionate and theophylline in mild-to-moderate asthma showed that fluticasone was more effective than theophylline.¹⁶

It is possible that theophylline-treated subjects may have achieved even better asthma control with higher doses. The near-equivalent efficacy of theophylline to aerosolized beclomethasone in the control of asthma was achieved with serum theophylline concentrations much lower than the usually stated therapeutic range of 10 to 20 mg/ml. About 55% of the theophylline-treated subjects had trough serum theophylline levels of less than 8 mg/ml. Thus oral theophylline is effective in treatment of asthma even when serum theophylline concentrations are low.

The dose of oral theophylline was adjusted by asthma specialists on the basis of individual clinical criteria and only secondarily on the basis of serum theophylline concentrations. Although higher theophylline doses and higher serum theophylline concentrations might have improved asthma control, it is likely that adverse effects and drop-out rates would have increased as well. The dropout rates in both groups were small, indicating that both theophylline and beclomethasone were well tolerated.

Significantly more subjects in the theophylline group experienced drug-related central nervous system disturbances (20% compared with 6% for the beclomethasone group; *p* < 0.001) and gastrointestinal disturbances (29% compared with 12% for the beclomethasone group; *p* < 0.001). Significantly more subjects in the beclomethasone group experienced drug-related oral candidiasis (5% compared with 0.5% for theophylline;

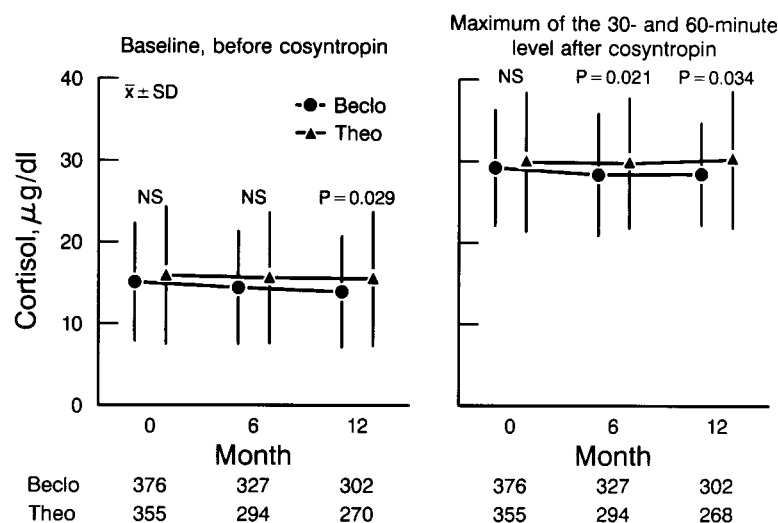


FIG. 5. Effect of beclomethasone and theophylline on morning plasma cortisol concentration and response to cosyntropin. Shown at bottom are number of subjects. Similar statistical analysis of subset of subjects who had never taken estrogens, birth control tablets, or glucocorticoids showed no significant difference in plasma cortisol concentration before or after administration of cosyntropin between treatment groups. NS, Not significant.

$p < 0.001$) and voice disturbances (5% compared with 0.3% for theophylline; $p < 0.001$). Thus the adverse-effect profiles of the two drugs were different, and more patients reported adverse experiences with theophylline. These adverse effects of aerosol glucocorticoids can be reduced by using a spacer to reduce oral deposition.¹⁷⁻¹⁹ The therapeutic outcome could also be optimized by adjusting the dose according to the severity of the disease and by adjusting the dose to suit changing circumstances during the course of treatment.^{4, 6, 7}

Unacceptable theophylline side effects might have been observed more frequently if all patients were receiving theophylline for the first time (almost half of these patients had used, and presumably tolerated, theophylline in the past) or if the dose of theophylline had been based on a predetermined peak theophylline blood level of 10 to 20 mg/ml rather than on acceptable control of symptoms. These patients were closely followed up by physicians experienced in treating asthma and knowledgeable about the difficulties involved in prescribing theophylline. Furthermore, theophylline blood levels were monitored to prevent overdose. Side effects might occur more frequently in a less structured setting.

It appears that this dose of beclomethasone dipropionate does have a systemic effect, at least in some persons. Analysis of the mean data from all subjects indicated a small but statistically significant reduction in morning cortisol levels after 6 and 12 months of treatment both before and after cosyntropin. The reduction (improvement) of methacholine bronchial reactivity in the beclomethasone group was small (less than one doubling dilution) and of uncertain clinical significance. This result contrasts with the report of Dutoit et al.⁵ that inhaled beclomethasone dipropionate aerosol spray was

considerably more effective than theophylline. The explanation for this discrepancy is not readily apparent. Despite their asthma being relatively mild, our patients were quite responsive to methacholine.

Maximum clinical improvement in both groups was reached after 2 to 4 weeks of treatment. Although this slow improvement was expected in beclomethasone-treated subjects, it was unexpected in those patients undergoing theophylline therapy. One possible explanation is the time necessary to determine optimum steady-state serum theophylline concentrations. However, steady-state theophylline levels were reached by day 4 to 7 (Table III). Although theophylline primarily is considered to be a bronchodilating agent, it also increases mucociliary clearance, increases diaphragmatic contractility, and has antiinflammatory properties. Theophylline reduces microvascular permeability, inhibits the late-phase bronchial response, and may inhibit lymphocyte and eosinophil infiltration of the airway.²⁰⁻²⁶ In vitro it inhibits antigen-induced mast cell histamine release and inhibits eosinophil degranulation. Thus another hypothesis is that 7 to 14 days of treatment are required for the full antiinflammatory effect of theophylline.

The maximum serum cortisol levels after cosyntropin stimulation were slightly lower in the beclomethasone-treated group compared with the theophylline-treated group. The clinical significance of this apparent suppression of cortisol production is unclear. However, in this study beclomethasone reduced the average velocity of growth in children by 1.5 cm/year.²⁷ Whether final height attained in adulthood is adversely affected by aerosolized beclomethasone is not known. Nevertheless, the potential adverse systemic effects of aerosolized glucocorticoids in pituitary-adrenal function, growth, and bone metabolism concerns many clinicians. For this

reason, published asthma guidelines recommend sodium cromoglycate as first-line therapy for children with mild persistent asthma.

In conclusion, both aerosolized beclomethasone and oral theophylline should be considered effective in the control of mild persistent or moderate asthma. In outcomes where there were differences, the differences were small but favored beclomethasone dipropionate. The risk/benefit profiles of these agents suggest that inhaled corticosteroids may be the preferred agent for most adult patients and children whose disease is not controlled by other antiinflammatory agents.

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APPENDIX

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