

Respiratory pathophysiologic responses

A methodological assessment of diurnal variability of peak flow as a basis for comparing different inhaled steroid formulations

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Background: A "survival" model offers certain ethical and practical advantages over alternative experimental designs if used to compare antiasthmatic inhaled steroid formulations. The model requires an objective daily measure of therapeutic effect (e.g., peak expiratory flow rate, which may be expressed as the lower of two daily measurements (LPF) or as diurnal variability (DVPF). The relative efficiency of these two measures is unknown.

Objective: This study was conducted to determine the relative efficiency of LPF and DVPF.

Methods: We analyzed data from a placebo-controlled comparison of an active inhaled formulation of budesonide versus an inactive oral formulation. The primary outcome measure in this design is the number of days from the time the test treatments start until a statistically significant deterioration occurs from an optimal asthma control value established at baseline.

Results: DVPF proved less sensitive than LPF; that is, fewer patients relapsed during the 8-week trial period: 32 versus 41, respectively. Also, the median interval until relapse was longer: 24 versus 9 days. With LPF, inhaled budesonide proved more effective than placebo or oral budesonide ($p = 0.03$), whereas DVPF failed to discriminate among the test treatments ($p = 0.38$). LPF correlated with all three symptom indices ($p \geq 0.003$) and two of three spirometric indices measured concomitantly ($p \leq 0.04$). DVPF did not correlate with any index ($p \geq 0.10$).

Conclusion: In this experimental model, LPF proved more sensitive and valid than DVPF as an indicator of differences in antiasthmatic potency between two inhaled steroid formulations. (*J Allergy Clin Immunol* 1996;98:555-62.)

Key words: Asthma, glucocorticoids, antiinflammatory agents, steroids, respiratory therapy, peak expiratory flow rate, respiratory function tests, clinical pharmacology

"Survival" type clinical trials that commence from a baseline state of optimal asthma control then measure the elapsed time to a specified outcome offer ethical, economic, and operational

Abbreviations used

DVPF:	Diurnal variability of peak expiratory flow
LPF:	Lower of 2 daily measures of peak expiratory flow
PEFR:	Peak expiratory flow rate

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advantages over alternative experimental designs for the purpose of comparing the antiasthmatic activity of one inhaled steroid formulation with another.^{1,2} Participants who experience an exacerbation of asthma during this type of trial are not necessarily required to continue an ineffective treatment for a predetermined fixed period. Instead, they have the option of completing the trial as soon as the specified end point is reached. This

TABLE I. Characteristics of patients in baseline week

Test treatments	Placebo	Oral budesonide	Inhaled budesonide
M + F (n)	8 + 8	9 + 6	11 + 5
Age (yr)	53.6 ± 4.1	51.1 ± 5.0	52.4 ± 3.4
Duration of asthma (yr)	19.2 ± 4.0	19.8 ± 3.7	24.8 ± 3.3
FVC (% pred)*	98.3 ± 4.3	98.1 ± 4.7	92.7 ± 5.6
FEV ₁ (% pred)*	78.4 ± 4.0	78.0 ± 5.6	73.3 ± 6.1
FEF ₂₅₋₇₅ (% pred)*	50.3 ± 4.7	51.2 ± 5.7	48.3 ± 5.5
LPF (L/min)	420.5 ± 28.7	417.7 ± 27.1	419.7 ± 37.3
DVPF (L/min)	26.0 ± 27.7	20.8 ± 11.1	37.4 ± 25.2
FAD	1.03 ± 0.38	0.36 ± 0.15	1.11 ± 0.36
SAD	1.97 ± 0.40	0.67 ± 0.19	1.28 ± 0.32
FID	3.16 ± 0.91	1.36 ± 0.43	3.26 ± 0.94

Values are expressed as means ± SEM.

FVC, Forced vital capacity; FEF₂₅₋₇₅, forced expiratory flow during middle half of FVC; FAD, frequency of asthma symptoms per day; Sad, severity of asthma symptoms per day; FID, doses of inhaled β-agonist per day.

*Percent predicted normal.

minimizes the loss of essential data, which may occur in fixed duration models because of premature dropouts triggered by symptom exacerbation. It also reduces the discomfort and risk to which patients may be exposed in clinical trials of fixed duration. This in turn facilitates patient recruiting and project approval by institutional review boards. Operating costs may also be reduced.

These advantages are critically dependent on the use of an objective index of therapeutic effect that can be measured every day (i.e., peak expiratory flow rate [PEFR]). The results may be expressed in terms of the low value of PEFR, measured morning and evening (LPF), or the diurnal variation between morning and evening values (DVPF).

Because the degree of DVPF is known to correlate significantly with the presence and magnitude of airway hyperresponsiveness to histamine or methacholine^{3,4} and because the latter appears to be a sensitive indirect measure of changes in airway inflammation,^{3,5} DVPF may be considered a surrogate measure of antiinflammatory activity in the airways.

For this reason and because the antiasthmatic effects of inhaled steroid drugs largely reflect their antiinflammatory properties,⁶⁻¹³ some regulatory jurisdictions and clinical investigators favor DVPF over LPF as the primary response index for studies designed to compare the therapeutic potencies of different formulations of inhaled steroid. However, no comparisons of the operational efficiency of these two alternative indices have been published.

Therefore we undertook this retrospective study to compare the performance of DVPF versus LPF when used as indicators of the occurrence of

asthma "relapse" after the withdrawal of patients from previously effective inhaled steroid treatment. To do this, we re-analyzed data from a published trial of this type in which a therapeutically active formulation of inhaled budesonide was compared in double-blind fashion with an inactive oral formulation of budesonide and a placebo.¹

METHODS

The test group comprised 47 adults with a clinical history of suboptimally controlled mild to moderate asthma characterized by variable wheezing and dyspnea responsive to β-agonist bronchodilator inhalant, diffuse wheezing on auscultation, obstructive pulmonary impairment, and no chronic airflow limitation.¹ Relevant demographic characteristics are shown in Table I.

The patients were initially treated for 4 weeks with doses of beclomethasone averaging 1.09 mg/day, inhaled through a 750 ml volume Vent-A-haler spacer (Glaxo-Wellcome, Inc., Mississauga, Ontario, Canada), with an optimized inhalation technique. The daily doses were adjusted individually at weekly clinic visits to maximize asthma control, as determined from symptoms and peak flow meter and spirometric indices, and to allow regular oral and inhaled bronchodilator treatment, if used, to be converted to "as needed" use. After completion of this lead-in period, the high-dose beclomethasone was abruptly reduced to 0.4 mg/day for 2 weeks. The last 7 days of this fortnight constituted the baseline week. At the end of this baseline week, the patients were randomly assigned to receive 8 weeks of treatment with one of three regimens: low-dose inhaled budesonide (0.4 mg/day) inhaled through a small-volume, extensible Inhalet spacer (Astra Pharma Production AB, Södertälje, Sweden); oral budesonide (1.4 mg/day); or placebo. The study was double-blind- and double-dummy-

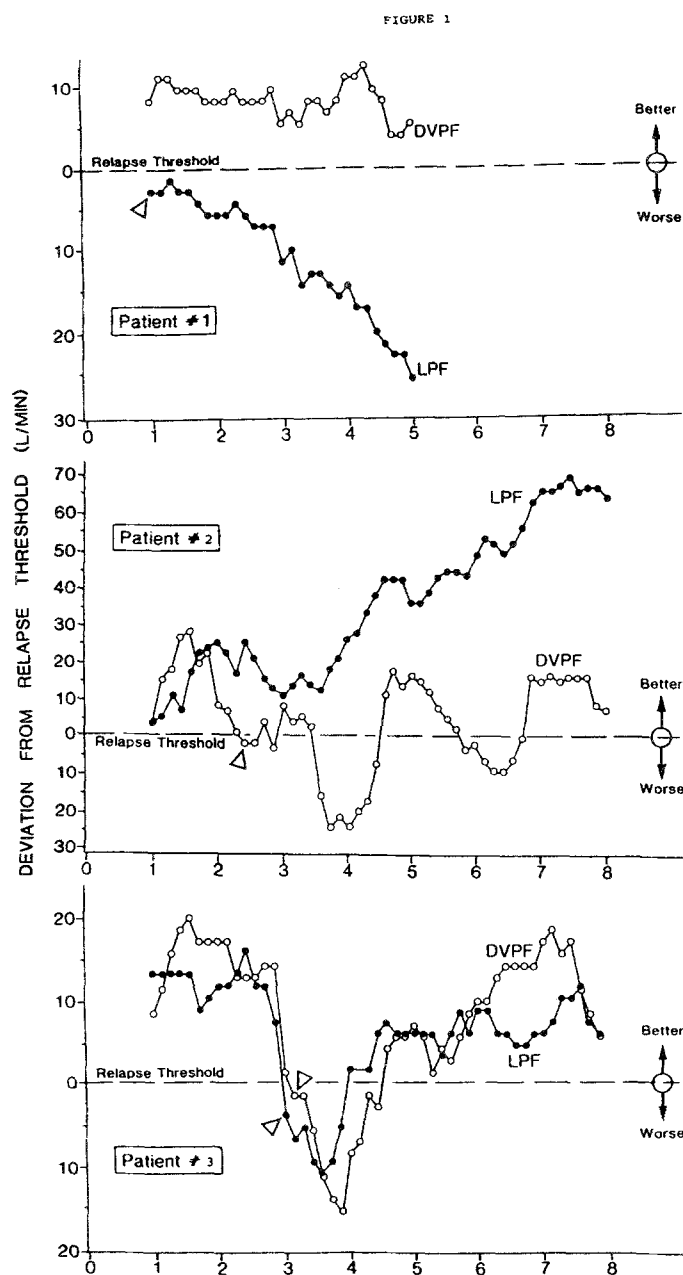


FIG. 1. Deviations from the threshold level of LPF (open circles) and DVPF (filled circles), for three representative patients, indicating a statistically significant deterioration in asthma control relative to baseline state. Given the formulas used to calculate the occurrence of asthma relapse as described in Methods, downward deviation indicates either a decrease in LPF or an increase in DVPF. Weeks of use of test treatments are shown on the abscissa. The first value that signifies advent of an asthma relapse is indicated by the arrowhead. The changes in LPF and DVPF observed in this study were not concordant in some patients.

controlled. Each patient received only one of the three test treatments.

Symptoms and the daily requirements for rescue doses of inhaled β -agonist were recorded in a current symptom diary. PEF was measured morning and evening with a Mini-Wright peak flow meter (Clement Clarke Inc.,

Columbus, Ohio), before bronchodilator inhaler use, and the highest of three readings was recorded. Spirometry was performed at weekly clinic visits. The mean values for these indices at baseline immediately before conversion to the test treatments are shown in Table I.

The primary outcome variable in this experimental

Relationship between Changes in LPF and DVPF up to Time of First Relapse

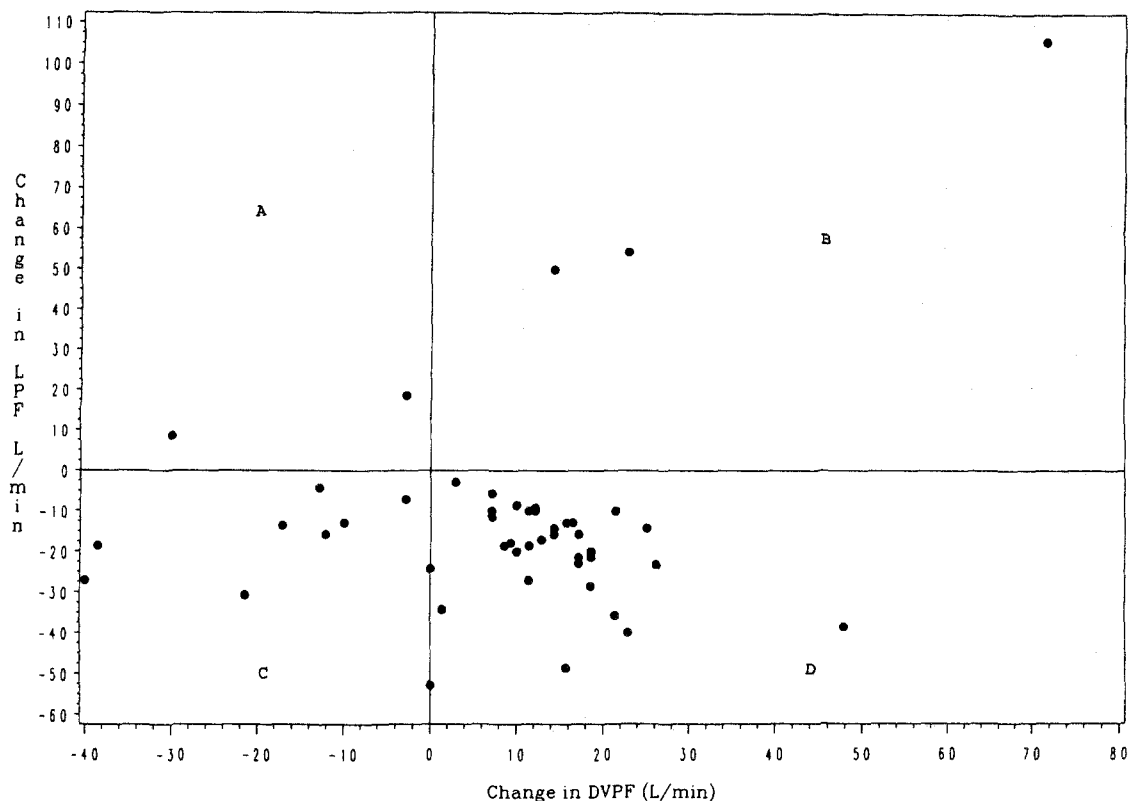


FIG. 2. Change in LPF and DVPF (shown separately for each patient) from baseline to time of initial asthma relapse, as defined in Methods. Increases in DVPF were not consistently related to a drop in LPF.

design is the number of days required to trigger an asthma relapse in each patient, as determined from changes in daily PEFR.

Alternative definitions of asthma relapse

In the original study, relapse was defined in terms of change in LPF.¹ For the purposes of this re-analysis, two alternative definitions of asthma relapse were computed from the same data base and compared. As described below, one is based on LPF and the other on DVPF.

Relapse based on LPF. The mean PEFR during the baseline week was determined for each patient and expressed in liters per minute. For each day of the study period that followed the baseline week, a moving average was calculated for the low PEFR recorded on that day and the 6 preceding days (A). Relapse was defined, separately for each patient, as the first day on which the moving average had dropped more than 2 standard errors below the mean low PEFR recorded during the baseline week (B). The formula for calculating the threshold level of LPF that signified asthma relapse is: Threshold level = $2 \times \text{SEM} - (A - B) < 0$.

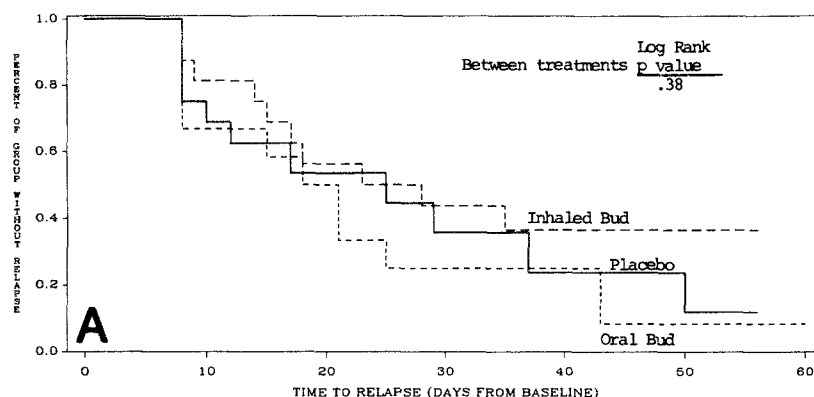
Relapse based on DVPF. For each patient, the mean range of PEFR (daily high minus daily low) during the baseline week was determined and expressed in liters per minute. For each day of the subsequent study period, a moving average of the range of PEFR values recorded on that day and the 6 preceding days was calculated (A'). Relapse was defined, separately for each patient, as the first day on which the moving average had increased more than 2 standard errors above the mean DVPF recorded during the baseline week (B'). The formula for calculating the threshold level of DVPF that signified asthma relapse is: Threshold level = $2 \times \text{SEM} - (B' - A') < 0$.

Representative examples of asthma relapse determined by these criteria are shown in Fig. 1.

Comparing the performance of LPF versus DVPF

The sensitivity of LPF versus DVPF as measures of change in asthma control was assessed by comparing their capacities to identify persons who experienced an asthma relapse after withdrawal of the previously effective

Time to Relapse based on DVPF for Oral vs Inhaled Steroid



Time to Relapse based on LPF for Oral vs Inhaled Steroid

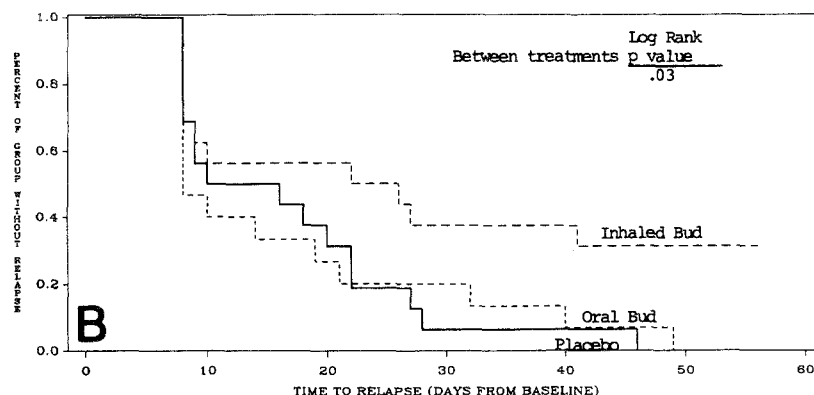


FIG. 3. Attrition of each treatment group caused by asthma relapse, as derived from the relapse data for DVPF (**A**) or LPF (**B**). LPF discriminated more efficiently than DVPF between active and inactive test treatments (i.e., inhaled budesonide vs placebo or oral budesonide), respectively.

tive treatment and also the median time interval until relapse became evident. Additionally, the two indices were compared with respect to their capacity to discriminate differences in efficacy among the three test treatments; *p* values were derived by the log rank test (SAS/Lifetest; SAS Institute, Cary, N.C.).¹⁴

To examine the validity of DVPF versus LPF as measures of change in asthma control, correlation coefficients and probability values were computed to quantify the associations of each index with concurrent changes in spirometric measurements of airflow, the frequency and severity of asthma symptoms, and the need for rescue bronchodilator inhalant as recorded in the current symptom diaries.

RESULTS

The variability between LPF and DVPF, as separate indicators of asthma relapse, is illustrated for three representative patients in Fig. 1. In

patient 1, changes in LPF but not DVPF indicated the occurrence of asthma relapse. The reverse applied in patient 2. In patient 3 both indices varied concordantly.

The changes observed in the two indices after conversion to the test treatments are compared in Fig. 2 for each person in the study group. LPF declined in 42 of 47 patients (Fig. 2, *C* and *D*), and DVPF increased in 35 patients (Fig. 2, *B* and *D*). Although an overall correlation is evident between a declining LPF and an increasing DVPF ($r = 0.292$, $p = 0.046$), the changes in the two variables were not concordant in the 13 patients shown in quadrants *B* and *C* of Fig. 2. These patients, constituting 28% of the group, could be misclassified, depending on which variable is chosen to signify the advent of asthma relapse.

The survival curves for each of the three treat-

TABLE II. Correlations of relapse variables with other indices of asthma activity measured concurrently

Relapse variables	FAD	SAD	FID	FEV ₁	FVC	FEF ₂₅₋₇₅
LPF						
<i>r</i>	-0.44	-0.51	-0.43	0.27	0.30	0.35
<i>p</i>	0.002	0.0002	0.003	0.06	0.04	0.02
DVPF						
<i>r</i>	-0.09	-0.10	-0.01	0.21	0.24	0.10
<i>p</i>	0.57	0.52	0.95	0.15	0.10	0.51

Note: Because of the formulas used to calculate the relapse thresholds (see Methods), a negative correlation sign in this table signifies that symptoms increased in association with a fall in LPF or a rise in DVPF. The reverse applied with the spirometric indices (i.e., a positive sign signifies that the spirometric values increased in conjunction with a rise in LPF or a fall in DVPF).

FAD, Frequency of asthma symptoms per day; SAD, severity of asthma symptoms per day; FID, doses of inhaled β -agonist per day; FVC, forced vital capacity; FEF₂₅₋₇₅, forced expiratory flow during middle half of FVC.

ment groups, as determined from these relapse data, are shown in Fig. 3, *A* (DVPF) and Fig. 3, *B* (LPF). If DVPF was used as the criterion of relapse rather than LPF, fewer patients relapsed during the trial period (i.e., 35 vs 42, respectively). Also, the median intervals until relapse during oral budesonide, placebo, or inhaled budesonide treatment were longer with DVPF than with LPF: 18.5, 24, and 24.5 days versus 7, 12, and 23 days, respectively (compare Fig. 3, *A* and *B*).

The correlations of LPF and DVPF versus the other indices of asthma activity, measured concomitantly, are shown in Table II. As LPF fell, forced vital capacity, FEV₁, and forced expiratory flow during middle half of forced vital capacity also deteriorated; symptom frequency and severity increased; and rescue bronchodilator use rose as well (see correlation coefficients, Table II). There was no similar clinically meaningful association between the directional changes of DVPF and concomitant changes in asthma symptoms or airflows. LPF correlated significantly with all three symptom indices, ($p \leq 0.003$) and with two of the three spirometric indices ($p \leq 0.04$). DVPF did not correlate significantly with any index (Table II).

Among those patients who relapsed according to LPF, the 7-day mean of their diurnal variability of PEFR, expressed as a percent of the high value recorded each day, increased from 5.5 ± 0.96 (SEM) at baseline when asthma was well controlled to 9.48 ± 0.64 (SEM) at the time of asthma relapse.

DISCUSSION

In this placebo-controlled double-blind clinical trial, DVPF, determined from twice daily measurements of peak expiratory flow, proved less sensitive and less valid than LPF as an index of the variable course of chronic asthma (Fig. 3 and Table II).

Furthermore, when LPF was used as the primary response index to differentiate the three test treatments in terms of their antiasthmatic efficacy, low-dose inhaled budesonide treatment was found to be significantly more effective than the placebo and the therapeutically inactive oral formulation of budesonide with which it was compared ($p = 0.03$; Fig. 3, *B*). In contrast, DVPF failed to discriminate the active from the inactive test treatments ($p = 0.38$; Fig. 3, *A*).

These findings, with DVPF as an indirect or surrogate measure of airway hyperresponsiveness, are consistent with previously reported observations that direct measurements of airway hyperresponsiveness by histamine or methacholine challenge do not relate closely to the minimum medication requirements of patients with asthma,¹⁵⁻¹⁷ and therefore are not useful for determining such requirements.^{18, 19}

The findings are applicable to clinical trials that use a survival type model to compare different drugs, drug formulations, or inhalation devices used in the treatment of asthma with inhaled steroids. Whether similar limitations also apply to other experimental designs needs to be determined by appropriate methodological studies.

Other methodological considerations applicable to the survival model

In addition to choosing an efficient response index as discussed previously, other features of the study design may be critically important to the successful use of a survival model.

Avoiding functional antagonists. To ensure that daily PEFR measurements are free to vary, salmeterol and long-acting theophylline must be withdrawn during the lead-in period.

Minimizing carryover. It is important to avoid persistence of the effects of treatment used before entry to the study or during the lead-in period because this could postpone the occurrence of asthma relapse beyond the scheduled observation period, thus making it impossible to differentiate between the test treatments.

Carryover caused by previous inhaled steroid therapy (evidenced by long remissions after treatment withdrawal) has been observed in association with milder disease,²⁰ higher daily doses,²¹ and

longer treatment.²⁰ Our prototype study¹ was designed to avoid such confounding effects by: (1) excluding patients currently or recently receiving prednisone, cromolyn, or immunotherapy; (2) recruiting patients who had suboptimal asthma control as evidenced by currently active symptoms, subnormal FEV₁, and/or PEF values lower than their "personal best" as documented by a daily peak flow diary; (3) individualizing the increments of the daily dose of inhaled steroid during the lead-in period to ensure that no patient would receive doses higher than needed to secure optimal asthma control; and (4) limiting the duration of the optimal control achieved during the lead-in period to 3 weeks or less.

Optimizing asthma control. To expedite the acquisition of optimal control within the scheduled 4-week lead-in period used in our prototype study,¹ we sought an aggregate therapeutic response by combining the escalation of the daily dose of inhaled steroid²² with conversion to a four-times-daily dosing regimen,²³ introduction of a large-volume Vent-A-haler spacer, and intensive training in the techniques of efficient inhalation²⁴ and spacer use.²⁵ Patients were trained to inhale the drug slowly (25 L/min)²⁴ and were provided with an AiR incentive spirometer (AIRLIFE, Baxter Corp., American Hospital Supply Corp., Valencia, Calif.) with which to practice daily at home to ensure that the same inspiratory flow rate was maintained across all phases of the study.

Duration of baseline. Each of the treatments compared in the prototype study derived its threshold LPF value from the 7 days immediately before the baseline visit.¹ Lengthening this to 14 days would raise the cutoff threshold for LPF. In consequence, relapses would occur earlier after converting to the test drugs. This would not necessarily invalidate the comparison, but the associated symptomatic and spirometric changes would be smaller or perhaps absent in many cases, which could preclude validating the specificity of the index (LPF) on which the primary outcome relapse is based.

Statistical analysis

The threshold chosen to signify asthma relapse is important. We found that a less stringent threshold for relapse (i.e., a drop in LPF > 1 but < 2 SEM), coupled with statistically significant increases in symptoms and/or bronchodilator inhalant use, proved much less efficient than the criterion described in detail above (Unpublished data. Astra Draco Report no. 850-CR-0122. A compar-

ison of the antiasthmatic efficacy of inhaled vs oral budesonide).

It may be necessary to control in the analysis for any association found between baseline LPF and the interval until relapse. In the event that relapses fail to occur within the scheduled observation period, a conventional, fixed-length trial analysis may be applied to the data.

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