

Should we monitor peak expiratory flow rates or record symptoms with a simple diary in the management of asthma?

Jean-Luc Malo, MD, J. L'Archevêque, RT, C. Trudeau, RT,
Carlos d'Aquino, MD, and André Cartier, MD Montreal, Quebec, Canada

Background: Various means of monitoring asthma severity have been proposed to reduce morbidity and mortality rates. We compared two means of assessing asthma flare-ups: monitoring peak expiratory flow rate (PEFR) and keeping a symptom diary.

Methods: This was a crossover randomized study. After a 2-week baseline period during which spirometry and PC₂₀ methacholine were assessed, subjects were asked to record either PEFRs or to keep a symptom diary morning and evening for 6 months; a second baseline assessment separated the two periods. Subjects were asked to contact the study coordinator if the following occurred: (1) in the period of PEFR monitoring, daily fluctuations in PEFR were >20% or the absolute value fell to <80% of baseline or both occurred; (2) in the period of symptom diary monitoring there were nocturnal symptoms or a persistence of morning dyspnea after inhaled bronchodilator or a reduction in the duration of effect of the bronchodilator or it was impossible to go to work or school or all occurred. In that case they were asked to come to the hospital to confirm the flare-up through investigation for significant changes in FEV₁ or PC₂₀ or both. Forty subjects completed a 6-month symptom diary or PEFR recording period respectively, and 20 completed both.

Results: A total of 31 exacerbations were reported in 28 different subjects; three subjects had two flare-ups. Thirteen of 19 (69%) flare-ups were confirmed during the symptom diary period and 9 of 12 (75%) during PEFR monitoring. Nocturnal awakenings and morning falls in PEFR $\geq 20\%$ were the most frequent occurrences.

Conclusions: We conclude that a simple symptom diary may be as useful as serial PEFR monitoring in documenting asthmatic flare-ups. (*J ALLERGY CLIN IMMUNOL* 1993;91:702-9.)

Key words: Airway obstruction, bronchial diseases, lung diseases, bronchi

Increasing morbidity and mortality rates as a result of asthma have led physicians to develop means for monitoring its severity and for treating flare-up efficiently. Various guidelines have been prepared proposing modification in treatment based on symptoms

Abbreviations used

FEV₁: Forced expiratory volume 1 second
PC₂₀: Concentration of methacholine that causes a 20% fall in FEV₁
PEFR: Peak expiratory flow rate

From the Department of Medicine, Hôpital du Sacré-Coeur, Montreal, Canada.

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Reprint requests: J. L. Malo, MD, Department of Chest Medicine, Sacré-Coeur Hospital, 5400 West Gouin, Montreal, Canada H4J 1C5.

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or peak flow monitoring.¹⁻⁴ Knowing all of the symptoms is the first means of monitoring. Nocturnal symptoms are the hallmark of an unstable asthmatic situation and are present in subjects who are at risk of dying of asthma.^{5,6} Early morning symptoms and the reduction in the duration of the effect of bronchodilator medication are other symptoms that reflect an unstable asthmatic state.⁷ The inability to go to work or school is another key symptom suggesting more severe asthma. These symptoms have all been judged as essential in the assessment of asthma.⁴

Serial monitoring of airway caliber is another means of assessing the severity of asthma that has become more widely used since the late 1970s with the availability of simple and inexpensive devices for assessing peak expiratory flow rate (PEFR).⁸ Patterns of an unstable asthmatic state have been identified.⁵ Although increased fluctuations in PEFRs before asthma deaths have been noted,⁹ a case of asthma death not preceded by such fluctuations has been described.¹⁰ These cases are all anecdotal.

Clark et al.¹¹ recently summarized the available information on the serial use of PEFRs in asthma. One recent study examined the validity of a self-management plan for asthma with use of either PEFRs or symptoms. Both plans were as efficient in reducing doctor consultations and the proportion of subjects requiring oral steroids and short-term nebulized albuterol.¹² No objective confirmation of the asthma flare-up was obtained. In a recent study we found that a symptoms diary was more valuable than serial monitoring of PEFRs in the assessment of the efficacy of inhaled steroids.¹³ Serial PEFR assessment has been advocated in the follow-up of asthmatic subjects who are poor sensors of airway obstruction.^{14, 15} However, it may not be satisfactory enough to detect an exacerbation of asthma. Indeed, we recently showed that measurement of forced expiratory volume in 1 second (FEV₁) is better than measurement of PEFR in detecting airway obstruction during late asthmatic reactions.¹⁶ Increased bronchial responsiveness to pharmacologic agents may also reflect worsening of the asthmatic condition, as demonstrated after exposure to an antigen.^{17, 18} Changes in bronchial responsiveness reflect a modification in the asthmatic state,¹⁹ although they do not seem good enough to detect an asthmatic exacerbation; they should be coupled with other means such as assessment of spirometry.²⁰

To the best of our knowledge, no study has compared the validity of PEFRs and a diary of symptoms to detect exacerbations in asthma as confirmed by other objective testing, that is, significant changes in FEV₁ or bronchial responsiveness to pharmacologic agents or both. We hypothesized that a simple diary of symptoms could detect as many exacerbations as PEFR monitoring. The primary goal of the study was to compare the validity of a diary of symptoms and PEFR monitoring in detecting an asthmatic flare-up in comparison with the gold standards, which are significant changes in FEV₁ or, in the absence of significant changes in FEV₁, an increase in bronchial responsiveness to methacholine. The secondary goal was to evaluate the subjects' compliance with the two methods of assessment in an indirect way.

MATERIAL AND METHODS

Subjects

All subjects included in the study fulfilled the American Thoracic Society diagnostic criteria for asthma.²¹ Asthmatic subjects were selected in a consecutive way from subjects seen regularly at the asthma clinic at Sacré-Coeur Hospital, a tertiary care hospital. The subjects all required either inhaled beclomethasone or budesonide in addition to an inhaled β_2 -adrenergic agent or sustained-release theophylline derivatives or both. These were therefore subjects with more severe asthma. Subjects with a baseline PEFR less than 200 L/min were excluded from the study because it would have been difficult to determine what changes in PEFR were clinically significant.

Study design

The design of this study was randomized, crossover, and single-blind. Subjects were randomly assigned to one or the other of the methods of assessment (diary or serial PEFR monitoring). Although the study was single-blind, an "event" (i.e., an asthmatic exacerbation) was defined a priori with preset criteria.

Asthmatic subjects were asked to record their PEFRs or their symptoms in a diary morning and evening for two equal periods of 6 months. Assessments were performed for a period of 2 weeks, this being considered the baseline value for that method. At the time of entry in the study, the subjects were in a stable state (i.e., no awakenings as a result of asthma symptoms, no recent changes in the requirement for medication, no exposure to a known sensitizer besides house dust). FEV₁ and concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀) were then assessed on two occasions separated by 1 week at the same time of day at least 6 hours after taking an inhaled β_2 -adrenergic agent. FEV₁ had to be reproducible $\pm$ 10% from one visit to the next and PC₂₀ by a 3.2-fold difference, which is the upper limit for the reproducibility of the test in our laboratory.²² PC₂₀ methacholine was not assessed in subjects with a baseline FEV₁ less than 1.5 L.

Subjects were then seen 1, 3, and 6 months later to evaluate their status; or they were seen earlier in case of an event. The reason for switching then to the alternative means of assessment is that we wanted subjects to remain unaware and not to assume that one or the other of the means was superior in detecting flare-ups. Asthmatic subjects are generally seen every 3 months at our outpatient clinic. This did not therefore modify their usual habits. The study design had to be of the crossover type because it has been shown that there might be a contamination bias in subjects who are required to register both PEFRs and their symptoms at the same time.²³ Subjects' symptomatology can be influenced if they realize that they are having changes in PEFR values.

At the end of the first period (6 months or after a flare-up), subjects were switched to the other method of assessment, preceded by a 2-week baseline period in which PEFR or symptomatology was assessed together with FEV₁ and

TABLE I. Baseline anthropometric, clinical, and functional results of subjects who had an asthmatic flare-up

Subject no.	Sex	Age (yr)	Duration of asthma (yr)	Atopy	Medication	FEV ₁		PC ₂₀ (mg/ml)
						L	%pred	
1	F	37	4	+	BDT + Be 1000	2.9	94	1.5
2	M	28	4	—	BDT + Be 2000	2.1	54	1.1
3	F	60	21	—	BDT + Be 1500 + P 5	1.5	54	0.3
4	M	63	4	—	BDT + Be 1600	3.6	109	16
6	M	43	5	D	BDT + Be 1500	3.3	88	0.06
7	F	28	28	+	BDT + Be 2000	2.0	71	0.6
8	M	44	44	+	BDT + Be 2000	2.9	77	0.2
12	M	53	3	—	BDT + Be 2000	1.9	61	0.6
16	F	22	17	+	BDT + Bu 1600	3.0	88	0.1
18	F	36	36	+	BDT + Bu 1600	2.4	92	1.0
19	F	47	47	—	BDT + Be 2000	1.6	60	0.5
21	M	41	34	+	BDT + Be 2000 + P 10	3.3	86	3.7
25	F	65	22	+	BDT + Be 1000	1.8	81	ND
27	F	48	19	—	BDT + Be 2000 + P 5	1.5	57	0.3
28	F	68	18	+	BDT + Be 2000	1.4	71	ND
31	F	62	15	—	BDT + Be 2000 + P 5	1.4	73	ND
34	F	57	37	+	BDT + Be 2000	1.5	56	Diluent
38	F	57	10	—	BDT + Be 1000	1.3	46	ND
41	F	30	5	+	BDT + Be 2000	2.6	81	ND
42	M	59	3	+	BDT + Be 2000	1.1	42	ND
44	F	49	46	+	BDT + Bu 1600	1.7	62	0.7
47	F	56	52	+	BDT + Bu 1600 + P 5	1.9	73	1.0
48	M	70	20	D	BDT + Be 400	1.3	75	ND
49	M	47	13	+	BDT + Be 2000	2.0	74	8
50	F	29	17	—	BDT + Be 2000 + P 5	3.3	112	0.5
53	F	47	15	+	BDT + Bu 1600	1.2	45	ND
57	F	37	19	+	BDT + Be 2000	1.3	48	ND
60	F	58	58	+	BDT + Be 1500	1.8	71	0.2
Mean		48	22			2.1	71	
SD		13	16			0.8	18	

Atopy, Present if one or more immediate skin reactions to a battery of 15 common inhalants; *D*, dermatographism; *BDT*, inhaled β_2 -adrenergic agent alone or with theophylline preparations; *Be*, inhaled beclomethasone with daily doses; *Bu*, inhaled budesonide with daily doses; *P*, prednisone with daily doses.

PC₂₀ methacholine was not assessed in subjects with a baseline FEV₁ < 1.5 L and in two subjects (no. 25 and 41) who were unable to attend.

PC₂₀. Nineteen subjects agreed to switch to the previous method for a third period. If there was an asthma flare-up, subjects were treated and stabilized before entering the baseline period for the alternative means of assessment (diary or PEFR).

Subjects were instructed not to use invented estimates for symptoms or PEFR if they forgot to do the assessment.

Definition and management of an event (flare-up of asthma)

The asthmatic subjects were asked to contact the study coordinator or his assistant if the following occurred:

In the case of the PEFR monitoring if PEFR prebronchodilator values (1) fluctuated by 20% or more in the same day (maximum – minimum prebronchodilator value and

mean daily value) three times in the same week²⁴; and/or (2) fell to 80% or less of the best value (morning or evening) recorded during the baseline period without significant improvement (back to mean baseline value) after taking an inhaled β_2 -adrenergic agent three times in the same week; and/or (3) fell to 50% or less of baseline on one occasion.

In the case of the diary if they had (1) nocturnal awakening as a result of asthma symptoms; and/or (2) shortness of breath in the morning, not improved 15 minutes after inhaling a bronchodilator; and/or (3) reduced duration (<4 hours) in the effect of an inhaled bronchodilator; and/or (4) inability to go to work or school because of asthmatic symptoms. If one or other of these symptoms was recorded once, the subject was asked to contact the study coordinator.

The subjects were then asked to come to the hospital on the same or the following day at the same time as the baseline assessment of FEV₁ and PC₂₀ at least 6 hours after taking an inhaled bronchodilator. If no significant changes were documented, they were asked to come back on the following day. Treatment was adjusted if changes >20% in FEV₁ and a >3.2-fold decrease in PC₂₀ were documented. Subjects were reassessed at weekly intervals until their functional status was back to baseline (FEV₁ $\pm$ 10% of baseline value and PC₂₀ back to $\pm$ a 3.2-fold difference from baseline). Subjects were then switched to the other method.

Means of assessment

The symptoms diary was similar to one recently used and reported by Malo et al.¹³ Symptoms that were recorded included the following: nocturnal symptoms, symptoms on awakening, and absence from work or school. PEFr was assessed by a mini-Wright (Clement Clarke International, Harlow, U.K.) peak flow meter and recorded three times; the best of two reproducible values ($\pm$ 20 L/min) being kept for analysis. Spirometry was assessed according to the American Thoracic Society guidelines,²⁵ and bronchial responsiveness was assessed according to a standardized method with use of methacholine instead of histamine.²⁶ PC₂₀ was interpolated from the individual dose-response curve drawn on a noncumulative logarithmic scale. A significant decrease in PC₂₀ (increase in bronchial responsiveness) was defined by a fall 3.2-fold or greater in PC₂₀ in comparison with the lowest of the two reproducible baseline values because this corresponds to the lower limit of the 95% confidence interval for the reproducibility of PC₂₀ in our laboratory.²² Predicted values for FEV₁ were obtained from Knudson et al.²⁷

RESULTS

Sixty adult asthmatic subjects (26 males; 34 females) (mean age $\pm$ SD, 47 $\pm$ 13 years) were enrolled. This included 40 atopic subjects (i.e., immediate skin reactivity to one or more of 15 common inhalants by the prick method). Baseline FEV₁ was 71% $\pm$ 17% predicted on entry to the diary period and 73% $\pm$ 18% predicted on entry to the PEFr period (NS). Mean PC₂₀ results were 0.8 and 1.1 mg/ml on entry to the diary and PEFr periods, respectively.

Subjects entered the study over an 18-month interval, at which time the study ended. Thirty started with the diary period and 30 with the PEFr period. Forty subjects finished the PEFr period, 40 the diary period, and 20 finished both periods. Mean durations of the diary and PEFr periods were 141 and 150 days, respectively. Three subjects did not complete the first 6-month period, two did not finish the second period, and four did not finish the third (optional) period because they did not want to carry on with the study, not because of an exacerbation of asthma.

Morning and evening symptoms were recorded for 88% and 87% of days, respectively, and on both occasions for 64% of days. Morning and evening PEFrs were recorded for 83% and 79% of days, respectively, and on both occasions for 55% of days.

Table I shows the anthropometric, clinical, and functional results of the 28 subjects who had at least one asthmatic flare-up during the course of the study. Six subjects took oral prednisone in addition to inhaled steroid preparations. All subjects except one (no. 48) took inhaled steroids at a dose that was 1000 μ g or greater. Nineteen (68%) had a baseline FEV₁ less than 80% predicted, and 16 of the 19 subjects who had a PC₂₀ assessment had values less than 2 mg/ml (moderate-to-severe bronchial hyperresponsiveness).

Tables II A and B give the details of flare-ups that were documented by the diary or PEFrs. A total of 31 exacerbations were reported: 19 by diary (61%) and 12 by PEFr (39%). Three subjects (no. 19, 28, and 38) had two flare-ups, one during each study period. Of the 19 exacerbations reported in diaries according to the criteria, 15 (79%) included nocturnal awakenings, alone or combined with one or more symptoms. Seven subjects reported a reduced duration of their inhaled β_2 -adrenergic agent and three, persistence of asthmatic symptoms after inhaling their β_2 -adrenergic agent. Four subjects had symptoms that precluded going to work or school. Morning falls in PEFr 20% or greater on at least three occasions occurred in all flare-ups. However, in no instance did these changes reach 50%. Daily fluctuations greater than 20% on at least three occasions happened in six instances.

Flare-ups were confirmed by significant changes in FEV₁ or PC₂₀ in 22 subjects (71%). Significant changes in FEV₁ happened in 19 of 22 (86%) of the confirmed flare-ups. The other three subjects had isolated increases in bronchial responsiveness. Flare-ups were confirmed in 13 of 19 subjects (68%) with the diary and in 9 of 12 subjects (75%) with PEFrs. By examining Tables II A and B, it can be seen that the episodes were not severe as judged by the changes in FEV₁ that were documented when subjects came to the hospital. Indeed, percentage falls in FEV₁ from baseline varied from 20% to 30% in 12 instances, from 31% to 40% in six, and were superior to 40% in only one subject (no. 2).

Nine of the 19 subjects (47%) who had a flare-up documented by the diary required two extra puffs or more of inhaled β_2 -adrenergic agent on at least 1 day (1 day in three subjects, 2 days in one, 4 days in two, 6 days in one, and 7 days in two subjects) in the week preceding the visit. This represents an extra need of inhaled β_2 -adrenergic agent by comparison with the

TABLE II A. Details on exacerbations of asthma

Subject no.	Flare-up no.	Means of assessment							Means of confirmation		
		Diary*				PEFR†			FEV ₁ changes	PC ₂₀ changes	Proven
		1	2	3	4	1	2	3			
1	1	+	—	+	+	NA	NA	NA	−20	NA	yes
2	1	NA	NA	NA	NA	−32 (350)	9	NA	−46	NA	yes
3	1	+	—	—	—	NA	NA	NA	−32	NA	yes
4	1	+	—	—	—	NA	NA	NA	−14	none	no
6	1	+	+	+	+	NA	NA	NA	−37	NA	yes
7	1	NA	NA	NA	NA	−36 (420)	19	NA	−16	10-fold	yes
8	1	NA	NA	NA	NA	−26 (475)	6	NA	−32	NA	yes
12	1	+	—	—	—	NA	NA	NA	−21	NA	yes
16	1	+	—	—	—	NA	NA	NA	−20	NA	yes
18	1	+	—	—	—	NA	NA	NA	−28	NA	yes
19	1	+	—	—	—	NA	NA	NA	0	3.2-fold	yes
19	2	NA	NA	NA	NA	−47 (330)	29	NA	−22	NA	yes
21	1	+	—	+	+	NA	NA	NA	−20	NA	yes
25	1	+	—	—	—	NA	NA	NA	−8	ND	no
27	1	—	—	+	—	NA	NA	NA	−21	NA	yes
28	1	NA	NA	NA	NA	−44 (200)	23	NA	−27	NA	yes
28	2	+	—	—	—	NA	NA	NA	−38	NA	yes

*Diary, (1) Nocturnal awakenings caused by asthma; (2) persistence of morning symptoms after inhaling β_2 -adrenergic agent; (3) duration of effect of inhaled β_2 -adrenergic agent <4 hours; (4) inability to go to work or school because of asthma.

†PEFR, (1) fall $\geq 20\%$ of the mean baseline value on three occasions (mean baseline value given in parenthesis); (2) daily fluctuations $\geq 20\%$ on three occasions; (3) fall in PEFR <50% baseline on one occasion.

NA, Not applicable; ND, not done.

FEV₁ changes had to be $\geq 20\%$ to confirm a flare-up; PC₂₀ was also assessed in 5 of 12 instances in which changes in FEV₁ were less than 20%; in one instance (no. 44) bronchoconstriction was elicited by inhaling diluent, confirming an increase in bronchial responsiveness.

2-week run-in period. As regards PEFR monitoring, as detailed in the Method section flare-ups were detected by fall to 80% or less of the best value (morning or evening) recorded during the baseline period without significant improvement (back to mean baseline value) after taking an inhaled β_2 -adrenergic agent three times in the same week. We had the chance to evaluate the number of days in which morning or evening PEFR fell by 20% or more. Of the 12 exacerbations of asthma documented by PEFR monitoring, eight (67%) had falls in PEFR on 1 (two subjects) or 2 days (six subjects).

DISCUSSION

This study shows that both a simple diary containing key questions and serial PEFRs can detect a comparable number of proven asthmatic exacerbations. Symptoms recorded in this study, that is, nocturnal awakenings, no improvement in morning symptoms after inhaling a β_2 -adrenergic agent, reduced duration of effect of inhaled β_2 -adrenergic agent, and inability to go to work or school because of asthma symptoms represent a reasonable reflection of an unstable asthmatic situation. Nocturnal awakenings caused by

asthma were reported in 79% of flare-ups. Others have also shown that nocturnal awakening as a result of asthma is a key feature of the condition; it being reported at least once a week in 74% of more than 70,000 asthmatic subjects treated by primary care physicians in the United Kingdom.²⁸ The reduced duration of the effect of a β_2 -adrenergic agent was reported in one third of the subjects.

PEFR monitoring has been advocated in the objective assessment of asthma since the 1970s with the availability of inexpensive and reliable portable devices and on the premise that some asthmatic subjects may be poor sensors of their condition.^{5, 29} The reduction in morning PEFR was shown in all subjects, whereas significant swings in PEFRs were far from being constant.

Most subjects who had a flare-up of asthma had significant changes in FEV₁. In only three instances did we find isolated changes in bronchial responsiveness without detecting changes in FEV₁. These data are along the same lines as results published by Josephs et al.²⁰ who showed that changes in bronchial responsiveness were not sensitive or specific enough in detecting asthmatic exacerbations.

TABLE II B. Details on exacerbations of asthma

Subject no.	Flare-up no.	Means of assessment							Means of confirmation		
		Diary*				PEFR†			FEV ₁ changes	PC ₂₀ changes	Proven
		1	2	3	4	1	2	3			
31	1	NA	NA	NA	NA	-34 (350)	19	NA	-36	NA	yes
34	1	+	-	-	-	NA	NA	NA	-4	ND	no
38	1	-	-	+	-	NA	NA	NA	-20	NA	yes
38	2	NA	NA	NA	NA	-44 (230)	21	NA	-27	NA	yes
41	1	NA	NA	NA	NA	-43 (470)	36	NA	0	ND	no
42	1	NA	NA	NA	NA	-38 (310)	4	NA	-10	ND	no
44	1	NA	NA	NA	NA	-24 (315)	8	NA	-13	Diluent	yes
47	1	+	-	-	-	NA	NA	NA	-5	ND	no
48	1	-	-	+	-	NA	NA	NA	-17	ND	no
49	1	+	+	-	-	NA	NA	NA	-4	2-fold	no
50	1	+	+	-	+	NA	NA	NA	-28	NA	yes
53	1	NA	NA	NA	NA	-40 (330)	20	NA	0	ND	no
57	1	-	-	+	-	NA	NA	NA	-39	NA	yes
60	1	NA	NA	NA	NA	-35 (275)	21	NA	-20	NA	yes

*Diary, (1) Nocturnal awakenings caused by asthma; (2) persistence of morning symptoms after inhaling β_2 -adrenergic agent; (3) duration of effect of inhaled β_2 -adrenergic agent <4 hours; (4) inability to go to work or school because of asthma.

†PEFR, (1) fall $\geq 20\%$ of the mean baseline value on three occasions (mean baseline value given in parenthesis); (2) daily fluctuations $\geq 20\%$ on three occasions; (3) fall in PEFR <50% baseline on one occasion.

NA, Not applicable; ND, not done.

FEV₁ changes had to be $\geq 20\%$ to confirm a flare-up; PC₂₀ was also assessed in 5 of 12 instances in which changes in FEV₁ were less than 20%; in one instance (no. 44) bronchoconstriction was elicited by inhaling diluent, confirming an increase in bronchial responsiveness.

The purpose of this work was not to assess the sensitivity and specificity of each instrument (diary or PEFR monitoring) in detecting asthmatic exacerbations. However, it is interesting to note that asthmatic exacerbations could be proved in a comparable proportion of subjects (68% and 75%, respectively) for whom there were changes in either the diary or in PEFR. For each instrument therefore, some "false positive" cases existed, that is, cases in whom symptoms or changes in PEFR occurred according to present criteria but in whom exacerbations of asthma could not be proved. Obviously, we did not have the means to assess the number of "false negative" cases. This would have supposed assessing FEV₁ and PC₂₀ daily, which is impossible in an interval of 6 months required for monitoring.

The criteria we used seemed to detect mild asthmatic flare-ups or asthmatic flare-ups or both at an early stage. The changes in FEV₁ that were recorded at the time of assessment in the hospital laboratory were in all instances but one between 20% and 40%. These could not be considered important changes, and it is assumed that they would not have required visits to an emergency department. Modifying the criteria for suggesting subjects contact the study coordinator (i.e., reducing the absolute percent changes in PEFR, the magnitude of daily fluctuations in PEFRs, and

adding more symptoms to the diary) might have resulted in more "positive" cases. It is interesting to note that in 47% of the documented flare-ups an increased requirement existed for inhaled β_2 -adrenergic agent. Falls in PEFR in 1 or 2 days of the week that preceded the visit, at which time the asthmatic flare-up was confirmed, occurred in 67% of cases. Therefore more sensitive criteria might have meant an earlier visit to the hospital laboratory. It is unknown, however, if at that specific time significant changes in FEV₁ and PC₂₀ or both could have been documented. A prospective study with different and hypothetically more sensitive criteria is needed to confirm this.

We assessed compliance in an indirect manner by asking subjects to record their symptoms or PEFRs using a design that tended to make them unaware that they were included in a study protocol. The number of days for which symptoms were recorded was slightly but not clinically significantly higher than for PEFR. This may reflect the fact that recording symptoms is easier than recording PEFRs. However, we had no direct means for assessing compliance. A proper evaluation of compliance with PEFR recording will be possible in the near future with the availability of instruments that record and store PEFR data for long periods. It would then be possible to have a satisfactory estimate of a subject's compliance. It is

our impression, however, that compliance with this recording tends to diminish with time because subjects feel that values are always stable. Subjects may even forget to record their values when they start having increased symptoms.

The design of this study did not allow for a synchronous reporting of flare-ups with the diary and PEFs, because the use of PEFs could have contaminated reporting of symptoms in the diary. The availability of instruments that could store PEF data in a blind way for the subject would make such a study possible. However, the duration of recording was long and similar with each method. We should have therefore expected a similar number of events to occur in each period. Finding an equivalent number of flare-ups with each means of assessment suggests that the efficiency of both tools in picking up asthma flare-ups is comparable.

We conclude that simple assessment of key symptoms reflecting asthma severity might be as useful as serial PEF monitoring in subjects with moderate-to-severe asthma. We indeed found approximately the same number of flare-ups in the two groups who were monitored with one or the other of these means. One has to remember that this conclusion would only apply if one used the criteria for defining a flare-up that were proposed, that is in the diary the appearance on at least 1 day of one or the other of the following symptoms: (1) nocturnal awakening as a result of asthma symptoms; and/or (2) shortness of breath in the morning not improved 15 minutes after inhaling a bronchodilator; and/or (3) reduced duration (<4 hours) in the effect of an inhaled bronchodilator; and/or (4) inability to go to work or school because of asthmatic symptoms. In PEF monitoring the criterion that proved most useful was a fall in morning or evening PEF 20% or greater three times in the same week. Other studies are needed to explore several aspects of this monitoring, as addressed recently by Clark et al.¹¹ They include the possible benefits for the patient, the relationship between the patient's subjective and objective estimates of airflow obstruction, determining which patients would benefit most from this serial monitoring, and the compliance with each method. It will soon be possible to assess the latter by use of devices that will be available in the near future.

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A controlled dose-response study of immunotherapy with standardized, partially purified extract of house dust mite: Clinical efficacy and side effects

Lars Haugaard, MD,^a Ronald Dahl, MD,^a and Lars Jacobsen, MSc^b

Aarhus and Hørsholm, Denmark

Background: Seventy-four asthmatic patients allergic to house dust mite were included in a double-blind, controlled study to establish the optimal maintenance dose of a standardized extract of *Dermatophagoides pteronyssinus* (Der p I) during 24 months of immunotherapy (IT).

Methods: The patients were given the following maintenance doses: 19 patients 10,000 standardized quality units (SQ-U) (group 10, 0.7 µg Der p I), 20 patients 100,000 SQ-U (group 100, 7 µg Der p I), 16 patients 300,000 SQ-U (group 300, 21 µg Der p I), and 19 control patients (group 0) had no injections. After 24 months bronchial challenge demonstrated a dose-related increased tolerance to Der p I, group 10 ($p = 0.003$), group 100 ($p = 0.0005$), group 300 ($p = 0.0007$), with no change in group 0 ($p = 0.6$). Patients given IT had a decrease in medication and peak expiratory flow score. In total, 2104 injections were given, and 3.5% were followed by a systemic reaction, defined as a fall 15% or greater in forced expiratory volume in 1 second within 30 minutes. A dose-response relation was demonstrated, with rates of systemic reactions in percent of injections; group 10, 0.56%; group 100, 3.30%; and group 300, 7.10% ($p < 0.0001$). No anaphylactic reactions occurred, and no late systemic reactions were observed. This study demonstrated a dose dependence of efficacy and side effects of IT in asthmatic patients. We suggest a maintenance dose of 100,000 SQ-U (7 µg Der p I) as an appropriate guideline for IT with house dust mite extract. (*J ALLERGY CLIN IMMUNOL* 1993;91:709-22.)

Key words: Dose response, immunotherapy, bronchial asthma, house dust mite allergy

From the Department of Respiratory Diseases, Section of Allergy University Hospital of Aarhus,^a Aarhus, and the ALK Research Group,^b Hørsholm, Denmark.

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Reprint requests: Lars Haugaard, MD, Department of Respiratory Diseases, Section of Allergology, University Hospital, Dk-8000 Aarhus, Denmark.

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Immunotherapy (IT) has been used in the treatment of allergic diseases since it was introduced by Noon¹ in 1911. Although it is generally accepted as efficient when administered under appropriate circumstances,^{2, 3} controversies still exist about optimum doses and regimens of IT.⁴ The efficacy has been shown to be related to dose.⁵⁻⁸ The value of a low maintenance dose has been comparable to placebo,⁹ and high doses seem to be necessary to achieve clinical efficacy.¹⁰ Because of this, high-dose regimens of IT