

Nocturnal awakening caused by asthma in children with mild-to-moderate asthma in the Childhood Asthma Management Program

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Asthma, rhinitis,
other respiratory
diseases

Background: Nocturnal symptoms of asthma are a cause of significant morbidity and are included as a central feature in the categorization of asthma severity.

Objectives: Data from the Childhood Asthma Management Program were used to estimate the prevalence of nocturnal awakenings in 1041 children with mild-to-moderate asthma and to investigate the relationships between awakenings and peak flows, severity of asthma, and allergen sensitivity and exposure.

Methods: Daily diary care data were recorded during a 28-day interval in the Childhood Asthma Management Program screening process. The data on morning and evening peak flows, overall symptom codes, albuterol use for symptoms, and nocturnal awakenings for asthma symptoms were analyzed and compared with measures of personal characteristics, pulmonary function, and environmental characteristics of the patients.

Results: Three hundred fifty-one (33.7%) children experienced 1 or more night awakenings caused by asthma during the 28-day screening period while not taking any maintenance medications. Greater risk of night awakening was associated with more severe asthma (greater responsiveness to bronchodilator, airway reactivity to methacholine, peak flow variability, and use of albuterol for symptoms, all $P < .0001$) and atopy (increased IgE and allergy skin test reactivity, both $P = .0002$). Those with a positive skin test response to dog and a high level of dog allergen in the home had a greater risk of night awakening caused by asthma ($P = .01$), as did those with a positive skin test response to cat and a high level of cat allergen in the home ($P = .04$). Mean daily symptom code and use of albuterol for asthma symptoms increased in the 3 days immediately before a single awakening compared with in the 4 to 6 days before the awakening ($P = .02$ and $P = .01$, respectively); however, both morning and evening peak flows as a percentage of personal best were similar in both intervals. Mean daily symptom code and daily use of albuterol were greater in the 3 days after an awakening than in the 3 days before ($P < .0001$ and $P = .0002$, respectively). Mean evening peak flow percentage of

personal best the day after an episode of awakening was lower when a second consecutive awakening occurred than when there was only a single awakening ($P = .01$).

Conclusions: Nocturnal awakening occurred in one third of the children with mild-to-moderate asthma during a month of relative stability and appears to be an indicator of asthma that is becoming increasingly severe. (*J Allergy Clin Immunol* 2002;110:395-403.)

Key words: Nocturnal, asthma, Childhood Asthma Management Program, patient characteristics, peak flow rates

Nocturnal symptoms caused by asthma are a cause of significant morbidity^{1,2} and are included as a central feature in the categorization of asthma severity in the Expert Panel Report of the National Asthma Education and Prevention Program.³ Nocturnal symptoms are also associated with mortality from asthma.^{4,5} Early identification of worsening asthma has been a focus of asthma management.

Nocturnal asthma occurs in both adults⁶ and children,⁷ but the problem has not been well studied in children. Unlike the studies in adults, no study has defined the prevalence of nocturnal awakenings in children with asthma or examined relationships between awakenings and peak flow values in the evening, daily peak flow variability, severity of asthma as evidenced by airflow obstruction or methacholine reactivity, or allergen sensitivity and exposure. In addition, no study has examined the efficacy of monitoring peak flows in the prediction of nighttime asthma in children. It remains unclear how often daytime symptoms precede nighttime symptoms and whether they might serve as an indicator of the likelihood that problems might occur on a particular night.

The purpose of this study is to examine these issues by taking advantage of information obtained during the screening of children with mild-to-moderate asthma for enrollment in the Childhood Asthma Management Program (CAMP), a randomized controlled clinical trial of 3 treatments for mild-to-moderate childhood asthma.

METHODS

Patient screening process and data collection before randomization

CAMP was designed to evaluate whether continuous long-term treatment with either an inhaled corticosteroid or an inhaled corticosteroid drug safely produced an improvement in lung growth compared with treatment for symptoms only. The design and methods for CAMP have been described previously.⁸⁻¹¹ Entry criteria

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Abbreviations used

CAMP: Childhood Asthma Management Program
GEE: Generalized estimating equation

were designed to include patients with mild and moderate asthma. In addition, the clinic coordinators rated asthma severity as mild or moderate on the basis, in part, of criteria in the Expert Panel Report of the National Asthma Education and Prevention Program.³ In the process of screening, patients with symptoms or medications prescribed for gastroesophageal reflux were excluded. During the screening process for CAMP, there was a 28-day interval of observation during which only albuterol on an as-needed basis was used.⁹ The process of preparing the children and parents for the 28-day screening interval, including learning the technique for peak flowmeter use and diary card completion, has been described.¹¹ During this interval, the parent or patient recorded daily diary data of morning and evening peak flows (best of 3 attempts), an overall symptom code for the day (0 = no asthma episodes; 1 = 1-3 asthma episodes, each lasting ≤ 2 hours and all mild; 2 = ≥ 4 mild asthma episodes or ≥ 1 asthma episodes that temporarily interfere with activity, play school, or sleep; and 3 = ≥ 1 asthma episodes that last ≥ 2 hours or result in shortened normal activity, seeing a doctor for acute care, or going to a hospital for acute care), number of puffs of albuterol for symptoms, and whether the child had been awakened by asthma the night before. A patient had to complete at least 24 days to demonstrate adherence with the protocol. Most (95.6%) patients had 27 to 28 days of data, with only 4.4% of patients having only 24 to 26 days of data. A limit of 1.5 nights or fewer per week awakened by asthma symptoms (average over the entire 28-day period) was imposed to ensure that patients with too severe asthma were not included in the trial. Three children were enrolled in CAMP despite having night awakenings more than 1.5 times per week on average in the 28-day screening period because of an error in the computer program used to evaluate eligibility. These children are included in these analyses.

Spirometry to define airway obstruction and responsiveness to bronchodilator (2 puffs of albuterol, 90 μ g/puff) was performed before the 28-day period, and methacholine challenge to define airway reactivity was performed at the end of the 28-day period. An overall assessment of severity was made by the clinical staff at the initial screening visit. Only patients assessed as having mild or moderate asthma were eligible for the study. Total numbers of peripheral blood eosinophils and total serum IgE levels were measured at the end of the 28-day screening interval. Sensitivity to environmental allergens (10 standard skin prick tests were done at each clinic, with up to 10 more added on the basis of local allergen prevalence; all allergens were considered in the analyses), levels of 6 environmental allergens present in home dust, and exposure to environmental tobacco smoke were also assessed. Criteria for significant allergen exposure have been presented.¹²

Statistical analyses

Personal, pulmonary, and environmental characteristics of patients with night awakenings. Logistic regression was used to investigate the association between those ever awakened at night by asthma during the 28-day screening period and the degree of airway obstruction before bronchodilator use (FEV_1 percent predicted and FEV_1 /forced vital capacity), bronchodilator responsiveness (ie, [FEV_1 after 2 puffs of albuterol – FEV_1 before 2 puffs of albuterol]/ FEV_1 before 2 puffs of albuterol $\times 100$), airway responsiveness to methacholine, duration of asthma, and other personal and environmental characteristics. The relative odds obtained from the logistic regression expresses the risk of night awakening for

patients with the specified risk factor compared with that of patients without the risk factor (binary risk factors) or the incremental risk per each unit change in the risk factor (continuous risk factors); that is, for risk factors that are continuous measures, the risk is expressed as a change in risk per unit of measurement. For several risk factors analyzed, the original unit of measurement was grouped by 10 to allow a more clinically useful specification of the change in risk (eg, risk per change in FEV_1 percent predicted is expressed as a change in risk per 10% change in FEV_1 percent predicted). Backward stepwise logistic regression was used to assess the net effect of these risk factors on night awakening caused by asthma when all were included in the model and to identify characteristics to use as adjustment variables in the analyses of associations between clinical indicators of asthma status and night awakening.

Use of daily diary data to examine risk of night awakening associated with clinical indicators of asthma status. Logistic regression was also used to investigate the risk of night awakening associated with various indicators of asthma status. Indicators of asthma status were constructed from 1- and 2-day sequences of diary data. The response for the regression was night awakening caused by asthma (yes/no). The regressors included in the model were the clinical indicator, age at randomization, race, sex, clinical center, and the risk factors identified in the backward stepwise regression analysis described above as associated with night awakening caused by asthma. Generalized estimating equations (GEEs) with robust variance estimation¹³ were used to account for the correlation between repeated observations from the same patient.

Use of daily diary data to examine change in indicators of clinical course before night awakening. Data from the 28-day screening period were reviewed for 7-day sequences consisting of 6 days without a night awakening caused by asthma, followed by a single night awakening caused by asthma. The initial 6 days were divided into two 3-day intervals: days 1 to 3 immediately preceding the single night awakening and days 4 to 6 preceding the single night awakening. Clinical indicators were calculated for each 3-day interval and were assessed for differences. A separate regression model was fit for each clinical indicator. The response for the model was the clinical indicator; regressors were a binary indicator variable for the 3-day interval (days 1-3 or 4-6) and age at randomization, race, sex, clinical center, and the risk factors identified by the stepwise regression, as associated with night awakening caused by asthma. GEEs with robust variance estimation were again used to account for correlation between observations from the same patient. Adjusted mean clinical indicators for each 3-day interval were computed from the regression model.¹⁴ The adjusted mean estimates and the expected indicator in the interval with the other regressors equated to their average values. The same approach was used to evaluate differences in clinical indicators for days 1 to 3 versus days 4 to 6 before 2 or more consecutive awakenings. Similar analyses were completed for 7-day sequences without any awakenings to provide insight on the changes in clinical indicators during periods without nocturnal asthma.

Use of diary data to assess whether night awakening is the consequence of problems or the start of problems. Diary data were also analyzed for the effect of night awakenings caused by asthma on the course of asthma after the night awakening. The approach was similar to that used to assess the change in the clinical indicators over the 6 days before an episode of night awakening. A model that included data from 3 types of multiday sequences (7 days without any night awakenings, 6 days of no night awakenings followed by a single night awakening, and 6 days of no night awakenings followed by ≥ 2 night awakenings) was constructed. Clinical indicators were calculated for the 4 to 6 days before a night awakening (before the seventh day for sequences without any night awakenings), the 1 to 3 days before a night awakening, and the day after the first night awakening and were

assessed for differences. Eight binary indicator variables were used to specify the interval (4-6 days before, 1-3 days before, and the day after) and type of sequence (ending in no night awakenings, ending in a single night awakening, or ending in ≥ 2 night awakenings). GEEs with robust variance estimation were again used because a patient could contribute more than one observation to the analysis. A similar approach was used to compare clinical indicators for the 3 days before an episode of night awakening with the same indicators for the 3 days after an episode of night awakening: the indicator for the 3 days before the episode was compared with the same indicator for the 3 days after the last night awakening in the episode.

Analysis software. All analyses were performed with either SAS software (version 6.12; SAS Institute, Cary, NC) or STATA software (release 6; Stata Corporation, College Station, Tex).

RESULTS

Prevalence of nocturnal awakening caused by asthma during the 28-day screening period when only albuterol as needed was used

Demographics of the 1041 CAMP patients are shown in Table I. The diary data from the 28-day period in the 1041 patients revealed that mean per-patient percentage of morning peak flow of less than 80% of personal best was 37.7% (range, 0%-100%), evening peak flow of less than 80% was 27.8% (range, 0%-100%), and morning or evening peak flow of less than 80% was 45.8%. The mean per-patient as-needed use of albuterol for asthma symptoms was 1.5 puffs per day, with a range of 0 to 7.4 puffs per day. The mean per-patient peak flow variability (mean relative difference between morning and evening peak flows) over the 28-day period was 0.11, with a range of 0 to 0.79.

Approximately 34% of the children (351 children) experienced one or more night awakenings caused by asthma during their 28-day screening period. The mean per-patient percentage of nights awakened by asthma during the 28-day screening period was 3.0% (range, 0%-25.0%). A total of 870 awakenings occurred. Most children had only 1 or 2 awakenings (13.3% and 6.8%, respectively), but 2.1% had 6 or 7 awakenings. Most of the 870 awakenings experienced by the children were isolated awakenings, with 61.7% occurring as single awakenings, but 22.8% occurred as 2 consecutive awakenings, 9.3% as 3 consecutive awakenings, and 6.2% as 4 or 5 consecutive awakenings. Defining an episode as occurrence of 1 or more consecutive night awakening, most children had no (66.3%) or only 1 (17.3%) episode of night awakening caused by asthma during their 28-day screening period, but 9.2% had 3 to 6 episodes.

Characteristics of patients with awakenings caused by asthma in the 28-day screening period

Risk of night awakening caused by asthma was similar for patients with different ages, ethnicity, income, and environmental exposures but was marginally less for male than for female patients ($P = .07$, Table II). Risk of

TABLE I. Demographic characteristics of the study population

No. of patients	1041
Age at randomization, y (mean $\pm$ SD)	8.9 $\pm$ 2.1
Ethnicity, no. (%)	
Non-Hispanic white	711 (68.3)
Non-Hispanic black	138 (13.3)
Hispanic	98 (9.4)
Other	94 (9.0)
Sex, no. (%)	
Female	420 (40.3)
Male	621 (59.7)
Annual income,* no. (%)	
<\$15,000	65 (7.4)
\$15,000-\$29,999	166 (18.9)
\$30,000-\$49,999	304 (34.6)
$\geq$ \$50,000	344 (39.1)

*Income is reported for participants enrolled at centers in the United States (because of wording of the questionnaire item, responses from Toronto participants could not be combined with responses from participants enrolled in the United States); income is unknown for 37 participants enrolled at centers in the United States. Annual income is the combined annual income, before taxes, of all members of the patient's household.

night awakening was higher for patients with greater atopy (by total eosinophil count, total IgE level, and skin prick testing) and more severe asthma on the basis of clinician's overall assessment. Risk of night awakening from asthma was similar for children, regardless of the level of prebronchodilator FEV₁ percent predicted but was marginally greater for those with a lower level of prebronchodilator FEV₁/forced vital capacity ratio ($P = .07$). A greater risk of night awakening was associated with increases in responsiveness to bronchodilator ($P < .0001$), airway reactivity to methacholine ($P < .0001$), peak flow variability ($P < .0001$), and use of albuterol for symptoms ($P < .0001$). Risk of awakening was similar for patients with and without exposure to environmental tobacco smoke, pets in the bedroom, or allergen levels in settled dust (data not shown). However, when sensitivity to an allergen was combined with the presence of allergen in the house (on the basis of allergen levels measured in settled house dust), those with a positive skin test response to dog and a high level of dog allergen in the home had a greater risk of night awakening caused by asthma ($P = .01$, Table II), as did those with a positive skin test response to cat and a high level of cat allergen in the home ($P = .04$). A similar analysis for dust mite allergen was only borderline significant ($P = .08$, Table II). The absence of similar findings for cockroach might simply be due to the smaller percentage of children with both sensitivity to cockroach and exposure to significant levels of Bla g 1.

Risk of night awakening and indicators of asthma status

Clinical indicators suggestive of unstable asthma were assessed for association with night awakening. Evening peak flow of less than 80% of personal best the day before, symptom code increase from 2 days before to the

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TABLE II. Risk factors for night awakening caused by asthma in the 28-day screening period: Demographic characteristics, measures of atopy and asthma severity, and environmental exposures

Risk factor	% with risk factor or mean	Logistic regression		
		Relative odds of night awakening*	95% CI*	P value†
No. of patients	1041‡			
Demographics				
Age at randomization, y (per year of age)	8.9	0.99	0.93-1.05	.7
Minority (yes vs no)	31.7	0.81	0.62-1.08	.15
Male sex (yes vs no)	59.7	0.79	0.61-1.02	.07
Income <\$15,000/y§ (yes vs no)	6.7	0.88	0.51-1.49	.62
Atopy				
Total blood eosinophils ≥ population median (400 cells; yes vs no)	50.8	1.55	1.20-2.01	.001
IgE, ng/mL (per 10-fold increase)	418	1.45	1.19-1.77	.0002
No. of positive skin test responses (per skin test)	5.4	1.06	1.03-1.09	.0002
Positive response to <i>Dermatophagoides pteronyssinus</i> or <i>Dermatophagoides farinae</i> (yes vs no)	48.4	1.46	1.12-1.88	.004
Positive response to dog (yes vs no)	22.7	1.87	1.39-2.52	<.0001
Positive response to cat (yes vs no)	48.9	1.56	1.20-2.02	.0008
Positive response to American or German cockroach (yes vs no)	33.9	1.38	1.05-1.80	.02
Positive response to <i>Aspergillus</i> species (yes vs no)	22.1	1.42	1.05-1.93	.02
Positive response to <i>Penicillium</i> species mix (yes vs no)	24.3	1.4	1.04-1.87	.03
Positive response to timothy grass (yes vs no)	46.6	1.24	0.96-1.60	.1
Positive response to short ragweed (yes vs no)	37.5	1.28	0.98-1.66	.07
Asthma severity				
Clinic staff assessed asthma as moderate (yes vs no)	52.2	1.63	1.25-2.11	.0003
Duration of asthma (per year)	4.8	1.01	0.96-1.06	.66
No. of days of prednisone in prior 6 mo (per day of use)	2.8	1.02	0.99-1.04	.22
Pre-BD FEV ₁ , % predicted (per 10% predicted)	93.7	0.94	0.86-1.03	.22
Pre-BD FEV ₁ /FVC ratio, % (per 10%)	79.7	0.87	0.75-1.01	.07
FEV ₁ BD responsiveness,¶ % (per 10%)	10.7	1.43	1.26-1.63	<.0001
FEV ₁ PC ₂₀ methacholine, mg/mL (per 2-fold increase)	1.1	0.83	0.77-0.90	<.0001
Days with morning or evening peak flow <80% of personal best, % (per 10%)	45.8	1.06	1.02-1.10	.004
Mean daily peak flow variability# ≥0.20 (yes vs no)	9.7	2.85	1.88-4.32	<.0001
Days with symptom code >0, % (per 10%)	53	1.19	1.13-1.25	<.0001
Days with albuterol use for symptoms, % (per 10%)	45.1	1.16	1.11-1.21	<.0001
Sensitivity and exposure				
Positive response to dog and Can f 1 >10,000 ng/g (yes vs no)	9.6	1.76	1.12-2.76	.01
Positive response to cat and Fel d 1 >8000 ng/g (yes vs no)	13.6	1.47	1.01-2.14	.04
Positive response to mite and (Der p 1 + Der f 1) >2000 ng/g (yes vs no)	26.8	1.3	0.97-1.74	.08
Positive response to cockroach and Bla g 1 >2000 ng/g (yes vs no)	3.2	0.54	0.23-1.27	.16
Positive response to <i>Aspergillus</i> species and/or <i>Penicillium</i> species and mold >25,000 colonies (yes vs no)	6.8	1.11	0.66-1.87	.7

*Relative odds is defined as ratio of the odds for those with versus the odds for those without the risk factor (yes vs no) or incremental odds for each specified change in the indicated risk factor (continuous).

†Wald χ^2 test for logistic regression with response variable is defined as ever awakened by asthma during the 28-day screening period (yes vs no), and regressor is defined as risk factor.

‡N varies from 879 to 1041 because of missing data.

§Participants enrolled at Toronto were excluded because their income responses could not be combined with responses from American participants as a result of the wording of the questionnaire item.

||Skin prick test responses are counted individually, regardless of relationship of allergens tested (eg, positive response to *D pteronyssinus* and positive response to *D farinae* counts as 2 positive test responses). Each child was tested with allergens listed above (10 in number) plus allergens considered to be relevant to the location of the CAMP clinical center (range, 0-10 in number).

¶FEV₁ BD responsiveness is defined as follows: [(Postbronchodilator FEV₁ – prebronchodilator FEV₁)/prebronchodilator FEV₁] × 100.

#Daily peak flow variability is defined as follows: (morning – evening)/[(morning + evening)/2].

day before awakening, any albuterol use for symptoms the day before awakening, night awakening 2 days before, and awakening the previous day or 2 days before were associated with increased risk of a night awakening compared with absence of the indicator (all $P < .0001$). The strongest risk factor for night awakening was prior night awakening: night awakening 1 and 2 days before increased risk nearly 14-fold, night awakening 1 day before increased risk 11-fold, and night awakening 2 days before increased risk 6-fold.

Conversely, clinical indicators suggestive of stable asthma were examined to estimate the risk of awakening after a day without asthma symptoms. When the evening peak flow was at least 80% of personal best, risk of a night awakening was only 65% of the risk of awakening after a day with evening peak flow of less than 80% of personal best ($P < .0001$). Risk of night awakening after a day with evening peak flow of at least 80% of personal best, no use of albuterol for symptoms, and symptom code of 0 for the day was 41% of the risk of awakening after a day with at least one of these indicators of unstable asthma ($P < .0001$).

Change in clinical course before night awakening

Clinical indicators in the days leading up to one or more night awakenings caused by asthma were examined. Mean daily symptom code and use of albuterol for asthma symptoms increased from 4 to 6 days before a single awakening to 3 days before awakening (0.67 vs 0.74 symptom code score [$P = .02$] and 1.72 vs 1.97 puffs per day [$P = .01$], respectively). Morning peak flow percentage of personal best (79.7% and 80.3%, $P = .42$), evening peak flow percentage of personal best (85.8% and 85.1%, $P = .23$), and peak flow variability (0.15 and 0.15, $P = .91$) were similar in both intervals. Mean daily symptom code (0.67 vs 0.78, $P = .02$) and use of albuterol for asthma symptoms (1.72 vs 2.09, $P = .01$) increased, and morning peak flow percentage of personal best (81.6% and 78.6%, $P = .01$) and evening peak flow percentage of personal best (85.8% vs 83.1%, $P = .05$) decreased in the 3 days before 2 or more consecutive night awakenings compared with the 4 to 6 days before the awakenings. In contrast, no differences were observed between clinical indicators for 4 to 6 days compared with the 3 days before a night without an awakening (data not shown).

Does nocturnal awakening signal the start of problems?

Table III displays clinical indicators for 4 to 6 days before an awakening, the 3 days before an awakening, and the day after an awakening for 6-day sequences, followed by a single awakening and 2 or more awakenings. Clinical indicators for 6-day sequences not ending in a night awakening are also shown. For sequences without an awakening, clinical indicators were similar for all 3 intervals of the 7-day sequences. For sequences ending in either a single awakening or multiple awakenings, mean

symptom code and mean number of puffs of albuterol increased across the 3 intervals, with the largest value for each indicator noted for the day after the night awakening. Both morning and evening peak flow percentage of personal best decreased across the 3 intervals only for sequences ending in awakening on 2 or more consecutive nights. Peak flow variability was similar across all intervals with a single awakening and 2 or more awakenings.

The clinical indicators for a single night awakening were compared with the clinical indicators for 2 or more night awakenings within the same interval (Table III). Indicators of asthma severity were more abnormal on the day after an awakening when followed by a second awakening than when there was no additional awakening: symptom code ($P = .01$) and albuterol use ($P = .05$) were greater, and mean evening peak flow percentage of personal best ($P = .01$) was lower.

Data for the 3 days before night awakenings began were compared with data for the 3 days after awakenings ended (Table IV) for episodes of a single awakening and episodes of 2 or more awakenings. Mean daily symptom code and daily use of albuterol were greater in the 3 days after the night awakenings ended than in the 3 days before the night awakenings began for both episodes consisting of a single awakening and episodes consisting of 2 or more awakenings. These patterns suggest that awakening is an indicator of increasingly severe asthma and not just an event associated with an increase in symptoms in the days before the event. Compared with the 3 days before the awakenings, neither morning nor evening peak flow percentage of personal best changed in the 3 days after a single awakening, but both were lower in the 3 days after 2 or more awakenings than in the 3 days after a single awakening (80.9% vs 74.8% [$P = .02$] and 84.9% vs 80.7% [$P = .002$], respectively). Symptom code, use of albuterol, morning peak flows, and evening peak flows in the 3 days after the episode of awakenings ended were significantly worse when there were awakenings on 2 or more consecutive nights compared with single awakenings. Peak flow variability was the same before and after awakenings, regardless of the number of awakenings that occurred in the sequence.

DISCUSSION

The data on nocturnal asthma obtained from the patients in the CAMP trial are the first on prevalence of nocturnal awakening in children with mild-to-moderate asthma and indicate that awakenings occur with significant frequency in children with mild-to-moderate asthma. Even during the 28-day period of screening for entry into the CAMP study, when there was relative stability with no exacerbations requiring prednisone, 33.7% of the 1041 children had at least one awakening, and 13.7% had 3 or more awakenings.

Patients with awakenings in the 28-day screening interval were more likely to be atopic, as noted by greater eosinophil counts, greater IgE levels, and greater frequency of positive skin test responses. Risk of night awaken-

TABLE III. Clinical indicators before and after awakening because of asthma

	N*	4-6 d before	1-3 d before	Day after first awakening†	P value‡
Mean symptom code§					
No night awakening	3423	0.57	0.56	0.57	.13
Single night awakening	221	0.64	0.71	1.42	<.0001
Awakened ≥2 consecutive nights	68	0.63	0.75	1.64	<.0001
Single vs ≥2 awakenings, P value		.93	.55	.01	
Mean puffs albuterol for symptoms§					
No night awakening	3433	1.4	1.36	1.33	.03
Single night awakening	221	1.56	1.81	3.01	<.0001
Awakened ≥2 consecutive nights	68	1.5	1.88	3.71	<.0001
Single vs ≥2 awakenings, P value		.8	.76	.05	
Mean morning peak flow, % best§					
No night awakening	3048	81.9	82.4	82.5	.002
Single night awakening	193	80.4	80.9	78.2	.03
Awakened ≥2 consecutive nights	60	82.9	80	74.4	<.0001
Single vs ≥2 awakenings, P value		.16	.61	.1	
Mean evening peak flow, % best§					
No night awakening	2954	85.5	85.8	85.9	.09
Single night awakening	196	86	85.1	83.9	.08
Awakened ≥2 consecutive nights	60	86.7	84	77.5	.0003
Single vs ≥2 awakenings, P value		.68	.55	.01	
Mean daily peak flow variability§,¶					
No night awakening	2774	0.11	0.11	0.11	.12
Single night awakening	180	0.14	0.14	0.15	.68
Awakened ≥2 consecutive nights	58	0.1	0.12	0.12	.32
Single vs ≥2 awakenings, P value		.01	.1	.08	

*No. of observations for each interval; N varies because of missing data.

†This is day 7 (no night awakening), the day after the night awakening (single awakening) or the day after the first awakening and the day before the second awakening (awakened ≥2 consecutive nights).

‡P value for difference between indicators for 4 to 6 days before, 1 to 3 days before, and the day after the first awakening (day 7 if no awakening).

§Means are adjusted for age, race, sex, clinic, log_e FEV₁ PC₂₀, FEV₁ bronchodilator responsiveness, prebronchodilator FEV₁ percent predicted, and sensitivity and exposure to dust mite. The latter 4 characteristics were identified in the backward stepwise regression as associated with night awakening when all are included in the model.

||P value for difference between clinical indicators for single versus 2 or more consecutive night awakenings within the time interval (4-6 days before, 1-3 days before, or the day after the first awakening).

¶Daily peak flow variability is defined as follows: (morning – evening)/[(morning + evening)/2].

ing was increased regardless of allergen tested, although grass, ragweed, and *Alternaria* species yielded only a borderline increased risk. The combination of a positive skin test response to dog and a high level of dog allergen in settled dust was significantly associated with greater risk of awakening, as was the combination of a positive skin test response to cat and a high level of cat allergen in settled dust. Patients with night awakenings also had increased lability of asthma, as noted by greater airway reactivity to both bronchodilator and methacholine, variability of peak flow measurement, symptom code, and albuterol use for symptoms. Taken together, the atopic characteristics and the observations of asthma lability in the children with awakenings suggest that allergen-mediated airway inflammation contributes to nocturnal instability of asthma and the associated awakenings.

The CAMP database also allowed detailed analysis of the clinical course and changes in peak flows around awakenings. Nocturnal awakening was associated with increased instability in clinical course, as evidenced by increased risk of night awakening in the presence of a variety of indicators of unstable asthma. The increases in risk tended to be small, except when the indicator includ-

ed prior night awakening. Risk of night awakening was reduced in the presence of indicators suggesting stable asthma (peak flow ≥80% of personal best, no use of albuterol for symptoms, and day without symptoms) by 35% to nearly 60%.

Prediction of night awakening is more difficult than finding patterns associated with awakenings. Although there were increases in symptom codes and albuterol use before single or multiple night awakenings from asthma, the changes in the indicators were small. Nocturnal awakening is followed by increased clinical instability, suggesting that an awakening is an indicator of future instability rather than just a result of previous instability. In the 3 days after a night awakening, symptom codes and use of albuterol were greater than in the baseline 3 days before the awakening (Table IV). Symptom code and albuterol use increased further on the day after even a single awakening (Table III). Although the data on symptom code and albuterol use the day after an awakening would be influenced by the awakening itself (on the day after the awakening, the symptom code would be increased because of the awakening, and albuterol used for symptoms during the awakening would be recorded), observing the

TABLE IV. Clinical indicators for 3 days before an episode of awakening caused by asthma* starts compared with 3 days after the episode of awakening ends by size of episode

	N†	3 d before episode starts	3 d after episode ends	P value‡
Mean symptom code§				
Single night awakening	273	0.75	0.98	<.0001
Awakened ≥2 consecutive nights	61	0.78	1.17	<.0001
Single vs ≥2 awakenings, P value		.7	.01	
Mean puffs of albuterol for symptoms§				
Single night awakening	273	1.97	2.3	.0002
Awakened ≥2 consecutive nights	61	1.93	2.87	.0002
Single vs ≥2 awakenings, P value		.87	.04	
Mean morning peak flow, % best§				
Single night awakening	244	80.4	79.5	.18
Awakened ≥2 consecutive nights	54	80.9	74.8	.02
Single vs ≥2 awakenings, P value		.81	.001	
Mean evening peak flow, % best§				
Single night awakening	237	84.8	84.8	.95
Awakened ≥2 consecutive nights	55	84.9	80.7	.002
Single vs ≥2 awakenings, P value		.93	.02	
Mean daily peak flow variability§,¶				
Single night awakening	223	0.14	0.15	.74
Awakened ≥2 consecutive nights	53	0.13	0.15	.17
Single vs ≥2 awakenings, P value		.23	.8	

*Episode is defined as 1 or more consecutive night awakening.

†No. of observations for each interval; N varies because of missing data.

‡P value for difference between clinical indicators for 3 days before versus 3 days after.

§Means are adjusted for age, race, sex, clinic, log_e FEV₁ PC₂₀, FEV₁ bronchodilator responsiveness, prebronchodilator FEV₁ percent predicted, and sensitivity and exposure to dust mite. The latter 4 characteristics were identified in the backward stepwise regression as associated with night awakening, when all are included in the model.

||P value for difference between clinical indicators for single versus 2 or more consecutive night awakenings within the time interval (3 days before or 3 days after).

¶Daily peak flow variability is defined as (morning – evening)/[(morning + evening)/2].

increased symptoms for the entire 3-day interval after the awakening supports the concept of decreased clinical stability after an awakening. It is also important to note that the diary data are self-reported. It is possible that the parents would be more aware of albuterol use or even more likely to record a greater symptom code and albuterol use in the period after an awakening.

The data on peak flows indicated that measurement of this pulmonary function might not be useful clinically in predicting an initial nocturnal awakening. Peak flows, both morning and evening flows, in the 3 days before either a single awakening or 2 or more consecutive awakenings were not clinically different than values for the 4 to 6 days before awakening. Peak flows the day after an awakening might be useful in predicting a second awakening, and thus a more severe change in clinical course.

Nocturnal asthma has been well studied in adults. Adults have a much higher reported prevalence of nocturnal asthma than that reported by the CAMP children. In a study including adult patients with all levels of asthma severity, Turner-Warwick⁶ reported at least 1 night awakening per month in 94% of the patients with asthma surveyed in the United Kingdom. Because severity scores were not given for these adults, a direct comparison of prevalence for awakening in adults reported by Turner-Warwick and children in CAMP cannot be made;

severity of asthma is likely to influence how often awakenings occur. Other than prevalence of awakening, findings in studies of nocturnal asthma in adults have been similar to those in the CAMP children. Fix et al¹⁵ found a highly significant association between nocturnal asthma and daytime symptoms characteristic of severe asthma, such as interference with daily activities. Martin et al¹⁶ demonstrated a significant correlation between nocturnal symptoms or awakening and severity of daytime airflow limitation and bronchial responsiveness to methacholine.

Our data indicate that nocturnal awakening is not uncommon, even in children with mild-to-moderate asthma. Children most at risk appear to be those with the most labile asthma and allergy with exposure to environmental allergens, particularly allergy to dog or cat when there is a large amount of dog or cat allergen in the environment. Thus the presence of nocturnal asthma might identify those children both at risk for severe exacerbations caused by lability of airway function and those who might most benefit from environmental control. Our data clearly indicate that changes in clinical symptoms and need for albuterol are more likely to predict nocturnal awakening than a decrease in peak flow. Prior night awakening is a risk factor for future night awakening, making close observation of a child after an awakening particularly important.

Asthma, rhinitis,
other respiratory
diseases

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