JAOA

ORIGINAL CONTRIBUTION

Day-night variation of airways status in sympathomimetic- and theophylline-treated asthma patients

ARTHUR C. BROWN, MPH
MICHAEL H. SMOLENSKY, PhD
GILBERT E. D'ALONZO, DO

Eleven diurnally active asthma patients having a history of nocturnal asthma and treated regularly with albuterol or metaproterenol alone or with twice-daily sustained-release theophylline were evaluated for day-night pattern in peak expiratory flow (PEF) and use of supplemental β-agonist aerosol for relief of acute asthma. Overall, significant day-night variation was observed in the supplemental use of β-agonist medication and in airway patency. The patients managed by albuterol or metaproterenol alone used supplemental β-agonist medication significantly more between 4 AM and 8 AM and also 8 PM and midnight in comparison to 4 PM to 8 PM; this was not true for those treated with both theophylline and β-agonist aerosol. In patients taking a β-agonist bronchodilator, the 24-hour mean PEF was greater than in those who also took theophylline, but the day-night variation in PEF was comparable. Supplemental isoproterenol use was significantly correlated with circadian amplitude of the PEF rhythm, but not with the 24-hour mean PEF. The greater the day-night variation in PEF, the greater the reliance on a supplemental β-agonist bronchodilator.

(Key words: Asthma, isoproterenol, albuterol, metaproterenol, sustained-release theophylline, peak expiratory flow, circadian rhythm)

The findings of recently published epidemiologic studies substantiate the clinical impression that asthma tends to be a nocturnal disease. For example, Dethlefsen and Repges[1] found in a large sample of more than 3000 asthmatic patients, temporarily removed from bronchodilator medications, that symptoms were 40- to 70-fold more common between midnight and 6 AM than during the afternoon. In addition, Turner-Warwick[2] reported that nearly 75% of a cohort of more than 7500 asthma patients were awakened from sleep because of nighttime symptoms at least once weekly, even while under treatment with equal-interval, equal-dose bronchodilator medications. The findings of Joad and associates[3] are consistent with those reported by Dethlefsen and Repges[1] and Turner-Warwick.[2] Patients treated with conventional equal-interval albuterol aerosol or sustained-release theophylline, alone or in combination, still experience nocturnal symptoms, particularly between 4 AM and 8 AM.

From the Schools of Public Health, Medicine, and Allied Health; and Center for Medical and Public Health Chronobiology, The University of Texas Health Science Center at Houston, Houston, Tex.

Correspondence to Gilbert E. D'Alonzo, DO, 925 Parkinson Pavilion, Broad & Tioga Sts, Philadelphia, PA 19140.

Previously conducted investigations of asthma medications have often relied on twice-daily (morning and evening only) peak expiratory flow (PEF) self-measurements or symptom diaries (or both) to assess patient status.[4-6] Our group has been interested in the more complete characterization of the day-night variation in airway status, in terms of the PEF as well as the need of β-agonist "rescue" bronchodilation. Because asthma is more common at night, even in patients treated with conventional equal-interval bronchodilators, one would expect to observe a lower PEF as well as a greater reliance on β-agonist aerosol rescue medication overnight in comparison with any other time of the day.

Previous experience and reports have documented the usefulness of self-assessed PEF several (four or more) times daily on a short-term basis to determine the circadian variation in airway status.[7-10] However, it is generally considered that patients are not likely to be compliant to such an assessment schedule for more than a few days.

A major difficulty in evaluating temporal patterns of supplemental bronchodilator aerosol use for the relief of acute exacerbation of asthma is securing reliable data. Patient's diaries are not necessarily accurate, especially when they must record the time of self-medication when awakened from sleep because of asthma. Spector and associates[11,12] and other investigators[13,14] have found that the metered-dosed-inhaler (MDI) nebulizer chronolog (Forefront Technology, Golden, Colo) accurately tracks the outpatient use of aerosol medication by asthmatic patients. This device enables the automatic recording of the clock time and calendar date of each actuation of the MDI. The results of previous investigations using MDI chronologs[11-14] suggested their suitability in studies examining the day-night pattern of supplemental β-agonist use for treating acute asthma attacks.

Methods

Subjects

Outpatients with asthma residing in the Houston vicinity were recruited for study. A medical history and physical examination were performed to eliminate those with cardiovascular disease and unstable asthma. Each person underwent a complete spirometric pulmonary function testing. Participants were to have been nonsmoking for at least 6 months, free of organic disease, and adhering to a diurnal activity/nocturnal sleep schedule. Moreover, they were to have a medical history of nighttime asthma, awakening at least once weekly. Other than sleep disruption due to asthma, no sleep abnormalities existed.

Table 1 shows the characteristics of the qualifying participants. The percent predicted baseline values for forced expiratory volumes at 1 second

Table 1
Characteristics of the Study Population

Subject No.	Sex	Age, yr	Height, cm	Weight, kg	FEV_1 Baseline (% predicted)	FEV_1 Isoproterenol (% predicted)
1	F	33	168	78	113	22
2	F	56	163	57	32	28
3	M	39	165	73	25	7
4	F	34	170	62	74	28
5	F	41	157	54	41	29
6	M	39	183	88	68	33
7	M	26	170	75	74	26
8*	F	43	163	105	112	12
9	F	19	160	64	112	24
10	M	65	168	70	104	17
11	F	59	160	66	102	15

*Assessed while maintained on morning prednisone (20 mg).

Table 2
Medication Summary

Subject No.	$ß_2$-Agonist inhaler	Anitcholinergic inhaler	Oral theophylline	Oral steroids
1	Yes	No	No	No
2	Yes	No	Yes	No
3	Yes	Yes	Yes	Yes*
4	Yes	No	Yes	No
5	Yes	No	Yes	No
6	Yes	No	Yes	No
7	Yes	No	No	No
8	Yes	No	Yes	Yes*
9	Yes	No	No	No
10	Yes	No	No	No
11	Yes	No	Yes	No

*Morning (20 mg) prednisone daily; patient 3 placed on steroid regimen during study.

(FEV_1) varied considerably. All but two patients had reversibility of airways obstruction by at least 15%. Participants were studied while adhering to the medications prescribed by their personal physicians (*Table 2*). All used inhalative β-agonist medications, either albuterol or metaproterenol, regularly. Generally, dosing was two puffs, three to four times daily at approximately equal intervals during diurnal activity. Seven of the 11 subjects also were treated with sustained-release theophylline formulations, primarily TheoDur (Schering, Kenilworth, NJ), taken twice a day, in the morning around breakfast and in the evening 12 hours later. Two of the 11 patients were under treatment with prednisone tablets, 20 mg in the morning.

Data acquisition

Participants were studied for 14 to 28 consecutive days (mean, 24.8 days) during autumn 1988. The PEF measurements (Mini-Wright Peak Expiratory Flow Meter, Armstrong Medical Industries, Inc, Northbrook, IL) were performed every 4 hours (7 AM, 11 AM, 3 PM, 7 PM and 11 PM) during the day and also when awakened at night with asthma, before the self-administration of β-agonist rescue medication. The best of three PEF measurements was recorded.

Each patient was provided with an MDI chronolog (Forefront Technology, Denver, Colo), which automatically recorded isoproterenol use for self-treating the breakthrough of asthma asymptoms. The chronolog is a small portable electronic device that accommodates any standard aerosol cannister. Each actuation of the MDI triggers a microswitch, which signals a microchip within the chronolog device to record the date and time of each actuation. Before patient use, each chronolog was tested in the laboratory for recording dependability by actuating each one six to ten times at different day and evening hours. Agreement between the diary-recorded and chronolog-indicated times was within 2 to 3 minutes.

Isoproterenol was selected for this research study because it has a potent, yet relatively short, duration of action. We anticipated that isoproterenol would more precisely characterize the effectiveness of the conventional β-agonist or theophylline (or both) treatments on airways status during specific time spans than would inhaled medications having a greater duration of effect.

Participants were instructed to use the medication in the MDI chronolog *only* for relieving acute symptoms of respiratory distress due to asthma, that is, tight chest, wheezing, and dyspnea. Too, they were instructed to record the clock time of each isoproterenol use in their provided daily diary. The participants also recorded information on health status as well as the time of going to sleep at night, awakening each morning, taking medications, exercising, and napping. The clock times of asthma symptoms and use of all medications also were reported.

Finally, the results of the PEF measures plus subjective assessment of the quality of sleep were documented. Sleep times for the patients as recorded in the diary confirmed that they were diurnally active. On average, men turned the lights out for sleep at 11:16 PM and awakened in the morning at 7 AM. For women, lights out was at 12:08 AM and awakening was at 7:34 AM. As a group, lights out was at 12:04 AM and awakening was at 7:23 AM.

Table 3
Patterns in Rescue Medication Use and Circadian Rhythm in Peak Flow

Subject No.	Actuations of MDI (isoproterenol)*	Mean asthma nights, No./wk	Peak expiratory flow†			
			Mesor,‡ L/min	Amplitude,§ L/min	Acrophase‖ (clock time)	Rhythm detection¶ (*P* value)
1	46	2.3	426	68.0	3:52 PM	<.001
2	82	1.0	155	11.8	4:26 PM	<.001
3	74	2.5	307	26.5	1:16 PM	<.01
4	281	1.8	241	45.3	6.32 PM	<.001
5	191	2.5	282	58.5	3:28 PM	<.001
6	53	2.5	430	28.9	1:24 PM	.03
7	34	2.3	498	58.3	3:32 PM	<.001
8	129	3.5	287	54.9	4:00 PM	<.001
9	12	0	376	35.6	7:32 PM	<.001
10	184	4.5	501	49.2	3:12 PM	<.001
11	48	0	385	42.5	3:36 PM	<.001

*Number of metered-dose inhaler (MDI) isoproterenol nebulizer chronolog actuations prorated to a 28-day duration.
†Peak expiratory flow ascertained by Wright flow meters.
‡Mesor = 24-hour, rhythm-adjusted mean.
§Amplitude = half the peak-trough variation during the 24 hours due to circadian rhythmicity.
‖Acrophase (peak time of rhythm by cosinor analysis) given in clock time.
¶Rhythm detection tested by evaluation of amplitude being nonzero in value.[15]

The patients were compensated for their study participation time. At weekly intervals for up to 28 days, they reported to the laboratory for the gathering of data from the MDI chronologs, review of the data diaries, and assessment of health status. The protocol was reviewed and approved by the Committee for the Protection of Human Subjects of the University of Texas Health Science Center.

Data analysis

Diaries as well as MDI chronolog records were used to examine the use of isoproterenol according to clock time. The data were evaluated in terms of isoproterenol use per each of six 4-hour spans during the 24-hour sleep-activity routine of the participants. The reliance on isoproterenol varied appreciably among subjects according to their perceived severity of asthma as well as the number of days studied. To facilitate the comparison of the 24-hour pattern in supplemental β-agonist bronchodilator use among patients, the data of each participant were normalized and prorated to 28 days. First, isoproterenol use per 4-hour span was expressed as a percentage of each participant's 24-hour total use. Then, the mean percentage distribution of reliance on supplemental β-agonist medication by each 4-hour span during the 24 hours was determined for the group. The data were analyzed as normalized values prorated to 28 days for a repeat-measures ANOVA for the main factors of subjects, treatment group (theophylline treatment vs nontreatment), and clock time.

The PEF and isoproterenol MDI data also were evaluated by single cosinor analysis to test for 24-hour periodicities in individual subjects.[15,16] A single 24-hour cosine curve was fit to the time series data by the method of least squares to objectively test for circadian rhythmicity and to yield the following indices: mesor, M (a time series 24-hour mean); amplitude, A (half the peak-trough variability); and acrophase, Ø (the crest time during the 24 hours in reference to local midnight).

The statistical significance of rhythm detection was determined by the F-statistic examining the variance accounted for by the approximation of the data by a 24-hour cosine curve in comparison with that of a straight line, essentially a test of the amplitude being zero.[15] If circadian rhythmicity was documented ($P < .05$), the M, A, and Ø were described with 95% confidence intervals. Population mean cosinors were also performed on the various data sets of interest to yield group M, A, and Ø.[16]

Results

Number of asthma nights

During the course of the study, asthma resulted in the disruption of sleep, on average,

(continued on page 327)

Table 4
Circadian Rhythmicity of Peak Expiratory Flow

Medication	Mesor,* L/min	Amplitude,† L/min	Acrophase,‡ time	*P* value
Albuterol or metaproterenol (n = 4)	450.3 (354.1–546.4)§	48.9 (8.0–89.9)§	4:08 PM (1:24–11:52 PM)§	.04
Metaproterenol or albuterol plus theophylline (n = 7)	298.1 (214.4–381.9)	35.1 (20.2–59.6)	3:40 PM (12:36–6:12 PM)	.01
All (N = 11)	353.0 (280.7–426.7)	40.0 (22.6–57.4)	3:52 PM (2:32–5:28 PM)	<.001

*Mesor = 24-hour, rhythm-adjusted mean.
†Amplitude = half peak-trough rhythm difference. *P* value by F test = 0.
‡Acrophase = peak time in clock hours (as hours and minutes from local midnight). All are determined by the fit of a cosine curve set to 24.0 hours.
§Numbers in parentheses are the 95% confidence interval.[15, 16]

more than two times per week (mean of 2.2 asthma nights per patient per week). However, *Table 3* shows considerable difference among patients, ranging from no bouts of nocturnal asthma in two patients to, on average, 3.5 and 4.5 times per week in two others.

Circadian rhythm in peak expiratory flow

Evaluation of the time series data of each participant by single cosinor analysis revealed statistically significant circadian rhythmicity ($P < .05$ to $P < .01$) of relatively high amplitude and with afternoon or early evening peak times for each (*Table 3*). For all patients, the PEF was reduced overnight, being lowest between 1 AM and 6 AM.

For the entire group of 11 participants, circadian rhythmicity in PEF was substantiated by population mean cosinor (*Table 4*). The timing of highest PEF, indicated by the acrophase, was at 3:52 PM; on average, the timing of lowest PEF was around 4 AM. The amplitude (peak-to-trough variation) amounted to approximately 23% of the 24-hour mean level. The population mean cosinor analyses of the PEF data (*Table 4*) for the seven patients treated with sustained-release theophylline plus metaproterenol or albuterol and those four patients treated with sympathomimetic aerosols alone, revealed comparable circadian patterns. However, those who were treated with albuterol or metaproterenol evidenced a much greater 24-hour mean PEF than did those whose treatment regimen also included theophylline.

Day-night pattern in isoproterenol dosing

For the entire group of 11 asthmatic patients combined, 956 inhalations of isoproterenol were delivered by MDI chronolog. Because the subjects usually took two inhalations of isoproterenol at a given time of need, these inhalations were equivalent to 478 dosings. Of these, 15 (3%) exceeded a 15-minute difference from the diary-reported times, 33 (7%) were unlogged in patient diaries, and 10 (2%) doses were recorded in diaries but not in the chronolog reports.

Figure 1 shows the group distribution of isoproterenol usage over the 24 hours according to each 4-hour segment of the day and night. The majority of isoproterenol inhalations were administered during the 12-hour span between 8 PM and 8 AM. Use of the bronchodilator was least between 4 PM and 8 PM. Isoproterenol self-dosings, specifically between 7 AM and 8 AM and again between 11 PM and 12 AM, accounted for 22.4% of the total.

Data evaluation by ANOVA did not reveal differences between theophylline users and nonusers in the number of MDI actuations. However, the difference in isoproterenol during the 24 hours was statistically significant. In particular, isoproterenol use was significantly greater ($P = .005$) for the entire group of 11 patients between 4 AM and 8 AM as well as 8 PM and midnight in comparison to between 4 PM to 8 PM. The subjects treated with albuterol or metaproterenol alone exhibited a significant ($P = .05$) difference in isoproter-

enol use between these same time spans. This was not the case ($P = .13$), however, for those asthma patients who were treated with albuterol or metaproterenol plus twice-daily sustained-release theophylline. Finally, although the use of isoproterenol between 4 AM and 8 AM by the non–theophylline-treated patients was greater than that of the theophylline-treated ones (*Figure*), the difference was of near statistical significance only ($P = .055$).

Discussion

In this investigation, 11 asthmatic patients with a history of nocturnal asthma were studied for circadian patterns in PEF and supplemental isoproterenol MDI use. The use of this "rescue" bronchodilator varied considerably among the participants when the data were normalized in terms of the number of MDI actuations per 28 days. If it is assumed that the number of actuations recorded by the MDI chronolog was representative of the number of actual drug inhalations, it is possible to examine the individual preference or need (or both) for the supplemental bronchodilator medication. Six of the patients (three treated with a sympathomimetic aerosol medication only and three treated with both theophylline and β-agonist aerosols) did not rely on isoproterenol to a great extent. These patients had a prorated 28-day isoproterenol use of between 12 and 82 actuations, no more than 41 doses consisting of two inhalations each. The remaining five participants evidenced between 129 and 281 depressions of the MDI chronolog, equivalent to between 65 and 140 doses of two inhalations each.

Those patients treated only with regular β_2-agonist aerosol bronchodilator medication had a statistically significant difference in the use of supplemental isoproterenol according to clock time, with usage significantly greater between 4 AM and 8 AM as well as between 8 PM and midnight compared with between 4 PM and 8 PM. However, those patients treated with a combined theophylline and regular β_2-agonist aerosol regimen did not have a significant day-night difference. Because an inclusion criterion for participation was a medical history of nocturnal asthma, perhaps the peak requirement for supplemental isoproterenol during the overnight period should not be unexpected. However, the inclusion criteria did not preclude a medical history of daytime as well as nighttime asthma.

In our study, a circadian rhythm in PEF was substantiated for the two subgroups of patients, theophylline users and nonusers. The 24-hour mean, amplitude, and peak time characteristics of the rhythm in PEF for these two patient subgroups are consistent with those reported in the literature.[17-19] The 24-hour mean PEF for the theophylline-treated, in comparison with the β_2-agonist aerosol–treated, participants was considerably depressed, with the difference in level being statistically significant ($P < .02$). The difference in PEF is not unexpected in that those for whom theophylline was prescribed, in general, had more severe asthma; their baseline spirometric evaluations (*Table 1*) generally revealed a lower FEV_1.

It was anticipated that participants with more severe asthma, those with the lowest baseline FEV_1 and percentage-predicted 24-hour PEF, would be the most reliant on supplemental sympathomimetic medication. The correlation of isoproterenol use with the percentage-predicted 24-hour mean PEF (mesor), however, was insignificant, the correlation coefficient being $r = -0.258$ ($P > .10$). This finding is consistent with that of Gong and coworkers.[14]

The literature suggests that the amplitude of the PEF circadian rhythm expressed relative to the 24-hour mean is a sensitive indicator of the instability of asthma. The greater the PEF amplitude, the greater the instability of the patient's asthma.[17-21] In this regard, the use of isoproterenol was related to the PEF circadian amplitude expressed relative to the 24-hour mean level ($r = 0.60$; $P = .034$). Thus, a moderate relationship between the use of supplemental isoproterenol and airway status is demonstrable in terms of the PEF circadian amplitude, but not the 24-hour PEF average while under treatment with twice-daily, sustained-release theophylline or β_2-agonist sympathomimetic bronchodilator medications (or both).

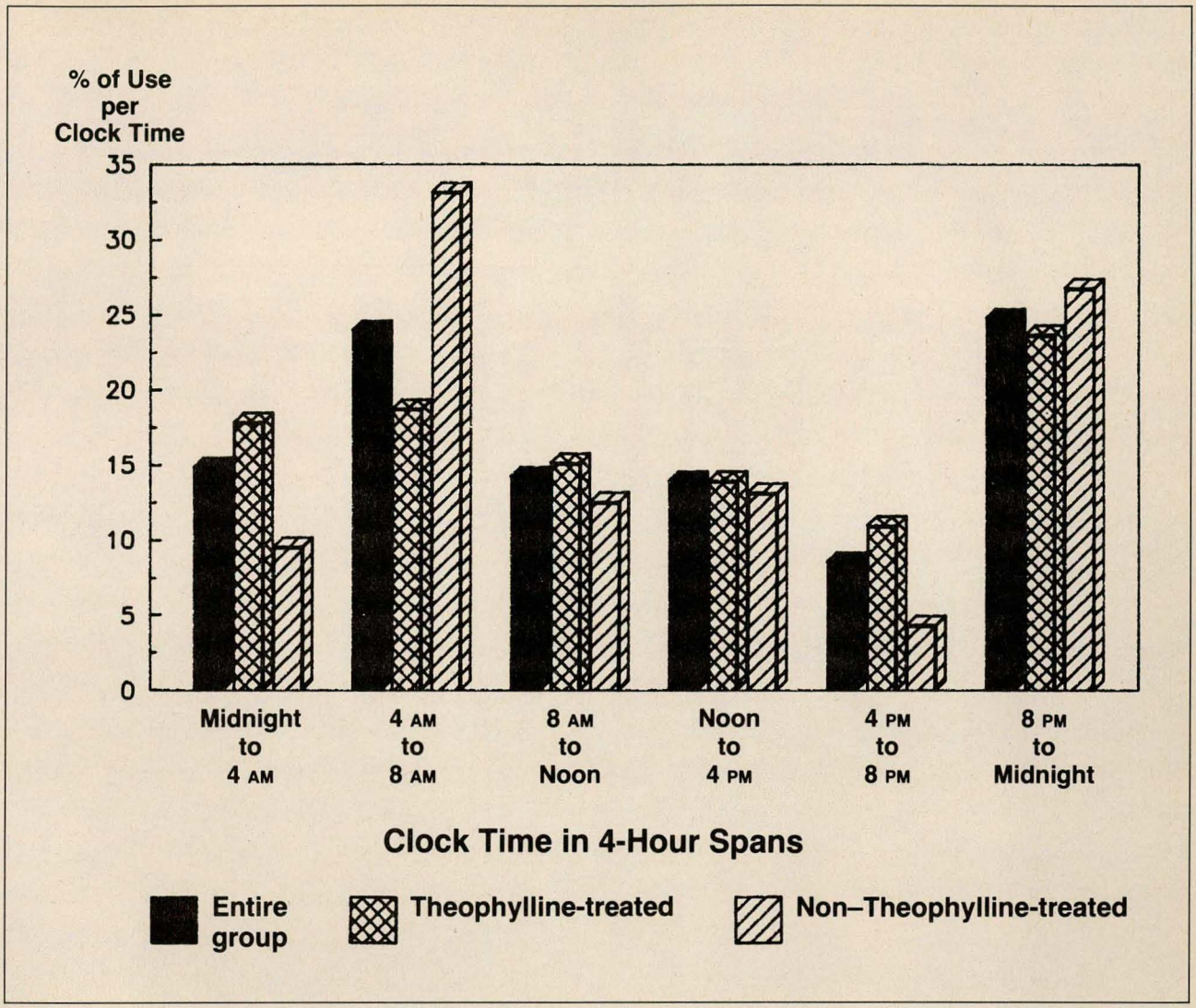

Figure. *Percentage distribution of supplemental isoproterenol use according to clock time in asthmatic patients regularly taking β_2-agonist aerosol medication (n = 4) alone or in combination with twice-a-day theophylline (n = 7).*

The absence of a *robust* association between isoproterenol use by patients and their 24-hour mean PEF level as well as circadian amplitude was unexpected. However, these findings are consistent with the hypothesis that the participants with more severe asthma, those who are often affected with symptoms, fail to appreciate the gravity of their asthma and to aggressively self-medicate themselves with sympathomimetic aerosols to relieve acute attacks. Even when the self-assessed PEF documented the presence of a large day-night variability in airway status, these patients apparently failed to recognize the need for self-medication.

The more severely affected patients relied on supplemental β-agonist medication to a lesser extent than those with milder disease. Perhaps, the former disregarded the instructions given them to use the MDI chronolog containing isoproterenol to medicate their acute symptoms of asthma, and instead or in addition used their conventional MDI β-agonist medication. However, this possibility seems unlikely because of the weekly review of compliance to protocol with participants.

Perhaps the patients were conditioned to usage of isoproterenol at specific times of the day or night based on previous knowledge of the temporal asthma-attack patterning. In this re-

(continued on page 332)

gard, 22% of the nebulizer chronolog actuations occurred between 7 AM to 8 AM (on awakening) and 4 PM and midnight (before bedtime). Although patients may have awakened in the morning with a tight chest or wheezing (or both) requiring sympathomimetic treatment, a longer-acting inhalative β-agonist seemingly would have been more appropriate, as would be the case before bedtime. This latter finding may indicate that patients were using their supplemental, instead of or in addition to their maintenance, β_2-agonist bronchodilator in anticipation of the acute exacerbation of asthma instead of for its relief. If this is proved to be the case, then more specific patient education concerning the actions and applications of different types of prescription and over-the-counter β-agonist aerosol medications seems warranted. Such issues regarding the use of supplemental MDI β-agonist therapy await future study on larger numbers of patients.

As in previous studies,[4-10,17-24] PEF proved to be useful in following the airflow status of asthma outpatients. It seems to be commonly thought that asthmatic patients are not likely to comply with monitoring protocols requiring more than two PEF measurements daily. Perhaps for these reasons, most studies on asthma patients have relied chiefly on protocols requiring morning (on awakening) and evening (around suppertime or bedtime) measurements to monitor airway status. For appropriate characterization of the circadian variation in PEF as well as airway status in general, several self-assessments per day are recommended.[7] In this investigation, participants were instructed to self-monitor their PEF every 4 hours during the daytime and, in addition, at night on awakening with asthma, throughout a study period lasting up to 28 days.

Each subject was compliant to PEF self-assessment; few data, less than 6%, were lost on the average. Moreover, agreement between the patients' diaries and MDI chronolog recordings of supplemental isoproterenol use was good; 88% of the diary entries were within 15 minutes of the MDI chronolog-documented uses and timings. This extent of agreement is comparable to that found by Gong and coworkers.[14] Greater disparity between daily diary and MDI chronolog reports, however, was reported by Spector and coauthors[12] in studies differing in objectives from the present one.

It is likely that the high compliance level achieved in the present study was due, at least in part, to the compensation of patients for their daily participation. However, other factors also are believed to be contributory. For example, at weekly intervals, the participants had scheduled appointments at the clinic. At those times, the data from the MDI chronologs were transferred to diskette, diaries reviewed with the patients, and PEF records checked. Finally, questions pertaining to the study and the health status of the participant were discussed. Undoubtedly, the weekly meetings, including the detailed review and discussion of the diary entries, resulted in a high degree of rapport between the investigators and the patients, presumably enhancing compliance to study procedures and methods.[24]

Comment

The day-night pattern in PEF revealed rather large variation in spite of the fact that the patients were under treatment with conventional bronchodilator therapy. During the afternoon, PEF was greatest, whereas overnight it was depressed. Overall, the day-night difference in PEF was substantial, being equal to 23% of the 24-hour mean level. Too, the use of isoproterenol for asthma was not randomly distributed over the 24 hours. In those asthmatic patients using albuterol or metaproterenol only, isoproterenol was used significantly more often overnight than during the day.

Conceptually, the temporal pattern in PEF and of supplemental MDI β-agonist use as determined in our group of patients is consistent with epidemiologic evidence substantiating asthma to be a nocturnal disease.[1,2] In this regard, our findings are consistent with those reported by Joad and associates,[3] who used diary entries to assess the efficacy of either albuterol or twice-daily theophylline (or both) during a series of 1-month study spans. This study found nocturnal asthma a problem, especially when treatment was with β_2-agonist therapy alone. When patients were treated

with theophylline, nocturnal asthma was still manifested but less frequently. The data of Joad and coworkers,[3] as do ours, indicate that the control of asthma, especially during the nighttime, in patients treated with conventional, twice daily, sustained-release theophylline or β_2-agonist aerosols (or both), is not optimal, because airway status still deteriorates overnight to a significant degree and nocturnal awakenings due to asthma persist.

Acknowledgments

The authors wish to acknowledge the support of the AB Astra (Lund, Sweden) and Purdue Frederick Pharmaceutical (Norwalk, Conn) companies for educational grants to make possible the described research.

References

1. Dethlefsen U, Repges R: Ein neues Therapieprinzip bei nachtlichen Asthma. *Med Klin* 1985;80:44-47.

2. Turner-Warwick DM: Epidemiology of nocturnal asthma. *Am J Med* 1988;85:6-8.

3. Joad JP, Ahrens RC, Lindgren SD, et al: Relative efficacy of maintenance therapy with theophylline, inhaled albuterol, and the combination for chronic asthma. *J Allergy Clin Immunol* 1987;79:78-85.

4. Barnes PJ, Greening AP, Neville L, et al: Single-dose slow-release aminophylline at night prevents nocturnal asthma. *Lancet* 1982;1:299-301.

5. Helm SG, Meltzer SM: Improved control of asthma in the office setting. A large-scale study of once-daily evening doses of theophylline. *Am J Med* 1988;85(suppl 1B):30-33.

6. Rivington RN, Calcutt L, Hodder RV, et al: Safety and efficacy of once-daily Uniphyl tablets compared to twice-daily Theo-Dur tablets in elderly patients with chronic airflow obstruction. *Am J Med* 1988;85(suppl 1B):48-53.

7. Gervais A, Reinberg A: The clinical significance of chronobiological methods for allergic asthma, in McGovern JP, Smolensky M, Reinberg A (eds): *Chronobiology in Allergy and Immunology*. Springfield, Ill, Charles C Thomas, 1977, pp 64-78.

8. Reinberg A, Gervais P, Chaussade M, et al: Circadian changes in effectiveness of corticosteroids in eight patients with allergic asthma. *J Allergy Clin Immunol* 1983;71:425-433.

9. Bruguerolle B, Philip-Joet F, Parrel M, et al: Unequal twice-daily, sustained-release theophylline dosing in chronic obstructive pulmonary disease. *Chronobiol Int* 1987;4:381-386.

10. Reinberg A, Levi F, Fourtillan JP, et al: Antihistamine and other effects of 5 mg mequitazine vary between morning and evening acute administration. *Annu Rev Chronopharmacol* 1984;1:57-60.

11. Spector SL: Is your asthmatic patient really complying? *Ann Allergy* 1985;55:552-556.

12. Spector SL, Kinsman R, Mawhinney H, et al: Compliance of patients with asthma with an experimental aerosolized medication: Implications for controlled clinical trials. *J Allergy Clin Immunol* 1986;77:65-70.

13. Perry GB, Chai H, Dickey DW, et al: Effects of particulate air pollution on asthmatics. *Am J Public Health* 1093;73:50.

14. Gong H Jr, Simmon MS, Clark VA, et al: Metered-dose inhaler usage in subjects with asthma: Comparison of nebulizer chronolog and daily diary recordings. *J Allergy Clin Immunol* 1988;82:5-10.

15. Halberg F, Johnson EA, Nelson W, et al: Autorhythmometry—procedures for physiologic self-measurements and their analysis. *Physiol Teach* 1972;1:1-11.

16. Nelson W, Tong YL, Lee JK, et al: Methods for cosinor rhythmometry. *Chronobiologia* 1979;6:305-323.

17. Smolensky MH, D'Alonzo GE, Kunkel G, et al: Day-night patterns in bronchial patency and dyspnea: Basis for once-daily and unequally divided twice-daily theophylline dosing schedules. *Chronobiol Int* 1987;4(3):303-317.

18. Hetzel MR, Clark TJH: Comparison of normal and asthmatic circadian rhythms in peak expiratory flow rate. *Thorax* 1980:35:732-738.

19. Hetzel MR, Clark TJH, Branthwaite MA: Asthma: Analysis of sudden deaths and ventilatory arrests in hospital. *Br Med J* 1977;1:808-811.

20. Hetzel MR, Clark TJH: Therapeutic implications of circadian rhythms in airway caliber in asthma, in Smolensky MH, Reinberg A, McGovern JP (eds): *Recent Advances in the Chronobiology of Allergy and Immunology*. Oxford, UK, Pergamon Press, 1980, pp 25-31.

21. Bonini S, Toccaceli F, Dato A, et al: The circadian assessment of peak expiratory flow as an additional tool for adequate treatment (and prevention) of bronchial asthma, in Smolensky MH, Reinberg A, McGovern JP (eds): *Recent Advances in the Chronobiology of Allergy and Immunology*. Oxford, UK, Pergamon Press, 1980 pp 33-40.

22. Neuenkirchen H, Wilkins JH, Oellrich M, et al: Nocturnal asthma: Effect of a once per evening dose of sustained release theophylline. *Eur J Respir Dis* 1985;66:196-204.

23. Beasley R, Cushley M, Holgate ST: A self-management plan in the treatment of adult asthma. *Thorax* 1989;44:200-204.

24. Sbarbaro JA: The patient-physician relationship: Compliance revisited. *Ann Allergy* 1990;64:325-331.