

Nocturnal Asthma: Mechanisms and Management

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Abstract

Nocturnal asthma, defined as an exacerbation of asthma at night, is associated with increases in symptoms and need for medication, increased airway responsiveness and worsening of lung function. Nighttime worsening of asthma has been recognized since the 5th century A.D. and is believed to be quite common, affecting a majority of asthmatics. The mechanisms of nocturnal asthma are intimately related to circadian rhythms, which influence inflammatory cells and mediators, hormone levels and cholinergic tone. Patients with nocturnal asthma symptoms may have greater nighttime activation of inflammatory cells and mediators, lower levels of epinephrine and increased vagal tone. In addition, underlying differences in the glucocorticoid receptor and β -receptors in these patients may diminish their ability to respond to therapy. While sleep appears to play a role in the pathophysiology of nocturnal asthma, it is not essential to it. Selective timing of medication can increase its efficacy and reduce its toxicity. Available therapy includes inhaled and oral corticosteroids, sustained-release theophylline, long-acting β -agonists, leukotriene-modifying agents and anticholinergic medication. The definition, epidemiology, potential mechanisms and management of nocturnal asthma are discussed in this review.

Key Words: Nocturnal asthma, chronobiology, chronotherapy, inflammation.

Introduction and Epidemiology

ASTHMA IS A CHRONIC INFLAMMATORY DISEASE of the airways, characterized by hyperresponsiveness to a variety of stimuli (1). It has long been recognized that asthma is worse at night. One of the earliest observations of a day-night pattern in asthma was made by Aurelianus Caelius in the 5th century A.D. (2). In the 1880s, Slater (2) wrote that "sleep favours asthma...spasm of the bronchial tubes is more prone to occur during the insensibility and lethargy of sleep than during the waking hours."

Nocturnal asthma is defined as a variable nighttime exacerbation of the underlying asthma condition associated with increases in symptoms and need for medication, increased airway responsiveness and/or worsening of lung function

(3). Generally, a reduction in peak flow or forced expiratory volume in one second (FEV1) of at least 20% is implicit in this definition. Approximately two-thirds of asthmatics suffer from nighttime symptoms (4). In a large study by Turner-Warwick involving 8,000 asthmatics (5), 75% awakened one night per week, 64% awakened 3 nights per week and 39% had their sleep disturbed on a nightly basis. Interestingly, of the patients who self-characterized their asthma as mild, 26% had nightly awakenings. The frequency of nocturnal awakenings did not appear to be related to a specific medication or combination of medications. There was also no particular trigger factor associated with nocturnal asthma, but allergic triggers were generally more frequent in this population than in patients without evidence of nocturnal asthma. In a study by Robertson et al. (6), 53% of asthma deaths occurred during the nighttime hours. The prevalence of nocturnal asthma is most likely underestimated. A better understanding of the mechanisms and management of this entity seems warranted.

Nocturnal Asthma and Chronobiology

The principles of chronobiology provide a framework for understanding nocturnal asthma.

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Chronobiology is the study of biological rhythms and their mechanisms (7). Every biological rhythm has a periodicity. Circadian rhythms have a periodicity of about 24 hours. It is well known that circadian rhythms influence disease processes and physiological events. For example, most myocardial infarctions occur in the early hours of the morning. Lung function (e.g., peak expiratory flow rate or FEV₁) is usually highest at 4 PM and lowest at 4 AM (7). The latter time is generally when asthma symptoms are most prevalent. Dethlefsen and Repges (8) studied a population of more than 3,000 patients (mainly asthmatics) and demonstrated that more than 90% of their dyspneic episodes occurred during the nighttime hours (Fig. 1). Clark and Hetzel (9) showed that diurnal variation in lung function exists in both healthy and asthmatic subjects (Fig. 2). However, the amplitude of variation is much greater in asthmatics, due to the greater dip in their peak expiratory flow rate at 4 in the morning. These investigators found that, on average, the diurnal variation was 8% in healthy subjects and 51% in asthmatics. A large circadian variation has been shown to precede sudden death and may or may not be reduced by anti-inflammatory therapy (10). In addition to the circadian variation in lung function in asthmatics, there is also a circadian variation in bronchial hyperresponsiveness (11). This variation in bronchial hyperresponsiveness is accentuated in subjects with noctur-

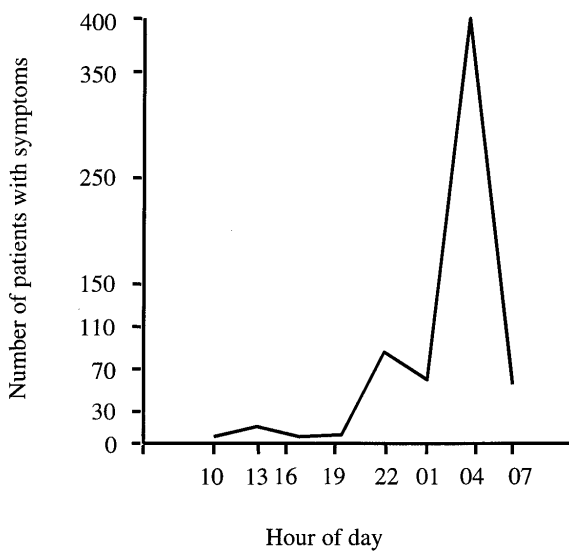


Fig. 1. Timing of dyspneic episodes in asthma. Hour of day is shown in military time. Asthma symptoms occurred most often between 2200 and 0700 hours, with a peak occurrence at 0400. Adapted, with permission, from reference 8.

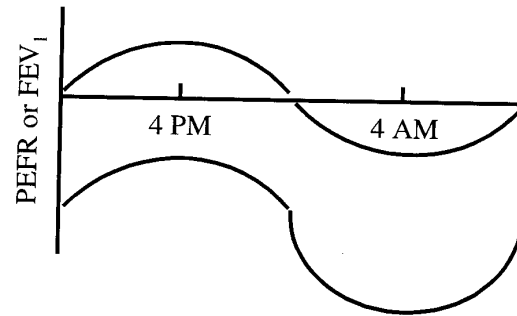


Fig. 2. Diurnal variation in lung function in healthy (top curve) and asthmatic (bottom curve) subjects. PEFR = peak expiratory flow rate; FEV₁ = forced expiratory volume in one second. Adapted, with permission, from reference 12.

nal asthma. Those with nighttime symptoms have an eightfold increase in bronchial reactivity overnight, as opposed to a twofold increase in reactivity in subjects without nocturnal asthma.

Potential Mechanisms of Nocturnal Asthma

Fig. 3 shows an overview of the potential mechanisms of nocturnal asthma and suggests that there is a complex interaction of many factors (12). These factors include a circadian variation in inflammatory cells and mediators, hormone levels, and vagal tone, all of which can enhance bronchial reactivity. Upper airway diseases such as chronic sinusitis and obstructive sleep apnea can modulate several of these factors.

Inflammatory Cells and Mediators

Approximately 40% of asthmatics exhibit a late phase reaction when exposed to allergen

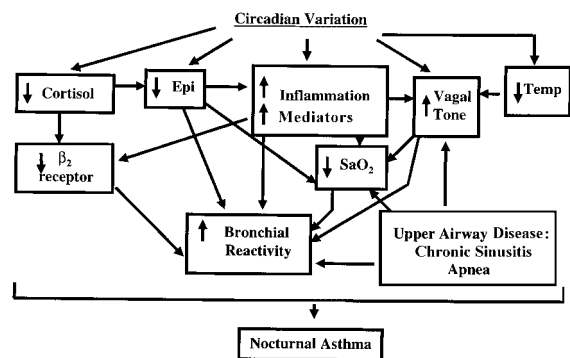


Fig. 3. Overview of potential mechanisms of nocturnal asthma. Temp = temperature; Epi = epinephrine; SaO₂ = oxygen saturation. Mediators: A variety of substances released from mast cells, eosinophils, lymphocytes, etc. Adapted, with permission, from reference 12.

(13). This reaction, due to airway inflammatory changes, is characterized by asthma symptoms which begin approximately 4 hours after the initial exposure and can last for 24 hours. The late phase is distinct from the early reaction, which generally resolves within one hour following exposure, and is due mostly to airway smooth muscle spasm (14).

Mohiuddin and Martin (15) studied the circadian basis of the late asthmatic response, hypothesizing that there might be a circadian variation in occurrence and severity. They challenged 10 asthmatic subjects with inhaled allergen at two time points, 8 AM and 8 PM. As can be seen in Fig. 4, all 10 individuals had an early phase reaction regardless of the time of challenge, but significantly more subjects had a late phase when challenged nocturnally ($p < 0.05$). This late phase was more severe, based on the reduction in lung function, tended to last longer and was followed by increased reactivity to methacholine at 24 hours after challenge.

In 1991, Martin et al. (16) extended this work by hypothesizing that inflammatory cells would be increased in bronchoalveolar fluid at night in patients with nocturnal asthma as opposed to those without nighttime symptoms. Seven patients with nocturnal asthma and 7 with non-nocturnal asthma underwent bronchoscopy at 4 PM and 4 AM. As shown in Table 1, the nocturnal asthma group manifested significant circadian variation in inflammatory cells, with increased total cells, neutrophils and eosinophils at 4 AM vs. 4 PM. These subjects also had an increase in most cellular elements compared to non-nocturnal asthmatics at 4 AM. Cell counts were not significantly different in the two groups at 4 PM. For all subjects, the overnight reduction in peak expiratory flow rate correlated with the overnight change in neutrophils and eosinophils.

Wenzel et al. (17) studied the contribution of leukotrienes to nocturnal asthma by measuring their levels at night in both bronchoalveolar

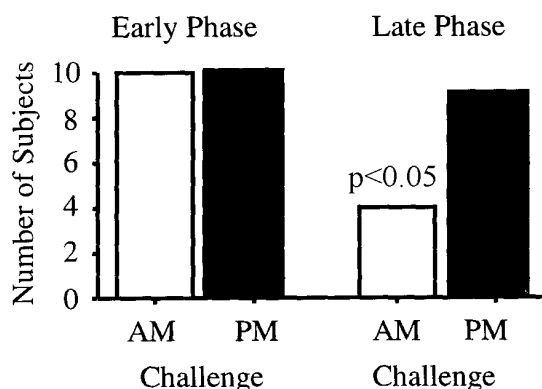


Fig. 4. Circadian variation exists in the late asthmatic response to allergen but not in the early response. Reproduced, with permission, from reference 15.

lavage and urine, in asthmatics with nighttime worsening and in healthy controls. Both bronchoalveolar and urinary leukotrienes were increased in the nocturnal asthma group. Leukotriene B₄ levels correlated significantly with the nocturnal fall in FEV₁.

The preceding studies suggest that worsening of asthma at night may relate, at least in part, to an increase in the inflammatory cells and mediators in the lung during the nighttime hours. Kraft and co-workers (18) investigated the site of inflammation in the lung, hypothesizing that the greatest circadian changes in eosinophilic airway inflammation would occur distally. This group performed fiberoptic bronchoscopy with both endobronchial (proximal) and transbronchial (distal) biopsy at 4 AM and 4 PM, in 11 subjects with nocturnal asthma and 10 with non-nocturnal asthma. Only the nocturnal asthma group had a greater number of eosinophils (per volume) at 4 AM than at 4 PM by transbronchial biopsy. The number of eosinophils obtained by endobronchial biopsy was low in both groups (regardless of time), as though these cells were migrating more distally in the lung. Alveolar tissue eosinophils corre-

TABLE 1
Bronchoalveolar Lavage Cytology in Patients With and Without Nocturnal Asthma

Cells (x 10 ⁴ /mL)	Non-nocturnal Asthma		Nocturnal Asthma	
	4 PM	4 AM	4 PM	4 AM
Total White Cells	18.3 ± 4.2	16.4 ± 2.0	24.0 ± 7.0	41.1 ± 9.9*†
Neutrophils	0.22 ± 0.06	0.2 ± 0.07	1.1 ± 0.6	3.7 ± 1.5*†
Eosinophils	0.29 ± 0.08	0.22 ± 0.07	0.5 ± 0.1	1.7 ± 0.7*†
Lymphocytes	2.4 ± 0.4	3.1 ± 0.7	7.0 ± 2.0	10.8 ± 3.6†

* $p < 0.05$ within a group between 4 PM and 4 AM. † $p < 0.05$ between groups at 4 AM. Adapted, with permission, from reference 16.

lated with the nocturnal decrement in lung function. This study thus supports the idea that the alveolar tissue is an important site of inflammation in nocturnal asthma.

More recently, Kraft et al. (19) evaluated the glucocorticoid receptor binding affinity and steroid responsiveness in subjects with nocturnal asthma at 4 PM and 4 AM, using radioligand binding and lymphocyte proliferation studies. They found that, compared with non-nocturnal asthmatics and healthy controls, those asthmatics with nighttime symptoms had a reduced steroid receptor binding affinity at 4 AM, which correlated with the decreased FEV1 at the same time. The nocturnal asthma group also demonstrated a diminished response to steroid treatment at 4 AM. These data indicated that patients with nocturnal asthma may have some unique features to their disease. For example, it has been proposed that differences in the cytokine milieu in these patients might lead to the observed alterations in the glucocorticoid receptor (20).

Humoral Changes

It is suggested that humoral changes may account for the phenomenon of worsening of asthma at night. Barnes and colleagues (21) investigated the idea that circadian rhythm may be important in the changes in airway tone in 5 nocturnal asthmatics and 5 healthy controls. Plasma hormone levels were measured at various times in both groups, and the effect of epinephrine infusion on lung function and on histamine level was assessed in the asthmatics. Interestingly, in the asthmatic cohort, the nadir in peak flow (4 AM) was associated with the nadir of the epinephrine level and the peak of the histamine level. Infusion of physiologic doses of epinephrine in these subjects diminished the overnight decline in lung function and also decreased the histamine level. The authors speculated that circulating epinephrine may act directly on α -receptors on bronchial smooth muscle or indirectly on β -receptors on mast cells to inhibit release of histamine. Other investigators (22), however, have not confirmed the finding by Barnes et al. of a nocturnal rise in plasma histamine level in patients with evidence of nighttime asthma.

Cholinergic Tone/ β -Agonist Function

It is known that increased vagal tone at night affects the heart. This change in vagal tone may also impact on bronchomotor tone

(23, 24). Morrison et al. (25) hypothesized that the parasympathetic nervous system may play a role in nocturnal asthma. They performed a placebo-controlled study of the effect of intravenous atropine on peak expiratory flow at 4 AM and 4 PM, in 10 subjects with nocturnal asthma. Atropine increased peak expiratory flow at both times, but the increase was significantly greater at 4 AM (Fig. 5). The circadian variation which existed with placebo was almost completely abolished after atropine. These results support the idea that the increased vagal tone at night may affect some patients with nocturnal asthma. In particular, patients with both asthma and obstructive sleep apnea syndrome may fall into this category, since obstructive sleep apnea and snoring can both increase vagal tone (26). It has been suggested that snoring is more prevalent in the asthmatic population (27), perhaps due to allergic rhinitis. Another potential contributing factor to nocturnal asthma, based on increased cholinergic tone, is gastroesophageal reflux disease (GERD) (28). The most widely accepted theory for this association is that acid reflux may stimulate vagal receptors in the lower esophagus, leading to reflex bronchoconstriction. Some authors, however, have minimized the role of GERD in nocturnal asthma. Tan and colleagues (29) studied the effect of esophageal acid on lower airway resistance in sleeping patients with nocturnal asthma (between the hours of 11 PM and 6 AM). Hydrochloric acid (0.1 N) was instilled via a nasogastric tube at a rate of 3 mL/min; a pH probe located above the gastroesophageal junction was used to confirm the presence of an acidic pH. Lower airway resistance was calculated from measured esophageal and supraglottic pressures, respiratory flow rates and tidal volumes. The authors found no change in airway resistance relative to periods of intraesophageal acid. A full discussion of this controversy exceeds the scope of this review.

In a pharmacological study by Szeffler and associates (30), the possibility of a circadian variation in leukocyte β_2 -adrenergic receptor density and function was examined in 7 patients with nocturnal asthma, 10 with non-nocturnal asthma and 10 normal controls. This group found that the number and physiologic function of β_2 -receptors was significantly decreased at 4 AM vs. 4 PM in patients with nocturnal asthma, compared to either of the other two cohorts. More recent work (31) has demonstrated that this phenotypic downregulation of β_2 -receptors can be explained by a specific polymorphism in the genetic coding block of the receptor (substi-

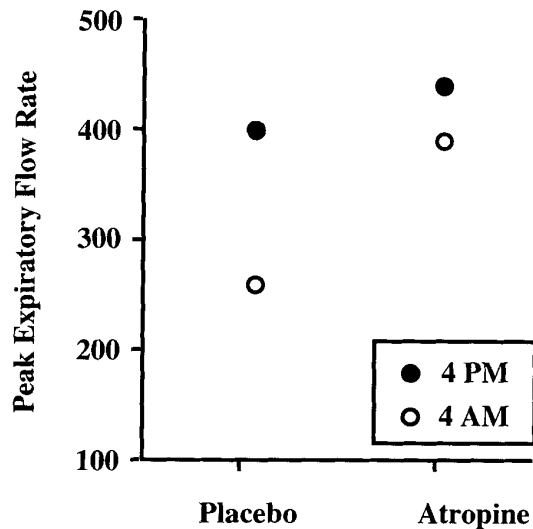


Fig. 5. Increase in peak expiratory flow rate with intravenous atropine versus placebo at 4 AM ($p < 0.0001$) and 4 PM ($p < 0.04$) in subjects with nocturnal asthma. The circadian variation in peak expiratory flow rate was significantly diminished after atropine ($p < 0.01$). Adapted, with permission, from reference 25.

tution of glycine for arginine at position 16). This polymorphism is more frequent in patients with nocturnal asthma as well as in those with more severe asthma.

The Role of Sleep in Nocturnal Asthma

The changes which characterize nocturnal asthma have been related not only to circadian events but also to sleep. Clark and Hetzel (9) studied shift workers with asthma and found that the worsening of their disease was always linked to the sleep cycle, regardless of the time of day. Subsequently, this same group repudiated their own findings (32). In 1989, Ballard et al. (33) measured airway resistance in patients with nocturnal asthma, from midnight to 6 AM on one night when the patients were kept awake and on another night when they were asleep. On both occasions, airway resistance was noted to increase; however, the increase was twofold greater when the patients slept during the study period. Other related studies have looked at the role of supine posture and of the consequent decrease in lung volume in nocturnal asthma, but most have dismissed these factors as irrelevant (34, 35). Work by Irvin and colleagues (35) suggested that the airway and parenchyma may become “uncoupled” during sleep in patients with nocturnal asthma. Normally, the airway wall is tethered to the surrounding lung tissue or

parenchyma, so that the two are interdependent. It is this interdependence which explains the normal hyperbolic relationship between lung volume and airway resistance; that is, as lung volume increases, airway resistance falls. In Irvin’s patients with nocturnal asthma, increasing lung volume at night during sleep did not lower airway resistance as anticipated. The authors suggest that the airway and parenchyma may become “uncoupled” during sleep in patients with nocturnal asthma, as a result of alveolar inflammation and additional neural influences.

Management of Nocturnal Asthma: Chronotherapy

Chronotherapy is based on the importance of biologic rhythms in the pathophysiology of medical conditions and uses the timing of medications to provide maximal efficacy and minimal toxicity (7). The standard dosing schedule of certain asthma medications already takes into account the known diurnal variation of symptoms, while in other cases, specifically timed regimens need to be ordered by the prescribing physicians.

Multiple investigations have examined the role of chronotherapy in administration of corticosteroids. In 1983, Reinberg et al. (36) performed a double-blind, placebo-controlled, randomized crossover study of 8 asthmatics given oral steroids in divided doses at 8 AM and at 3 PM or 3 PM and at 8 PM, over 8 days. Their results demonstrated more effective control of asthma symptoms and enhanced peak flow with the 8 AM and 3 PM schedule. Of note, the patients were not selected based on established criteria for nocturnal asthma. Almost a decade later, Beam and associates (37) examined the effect of a single dose of prednisone delivered at one of 3 specific times (8 AM, 3 PM or 8 PM) on asthma outcomes. The study was double blinded and placebo-controlled, with a crossover arm, and was directed at patients with nocturnal asthma. Only the 3 PM dose of prednisone resulted in overnight spirometric improvement (Fig. 6) and significant reduction in the number of all cell types ($p < 0.05$) in the 4 AM bronchoalveolar lavage cytology. The circadian variation in lung function associated with the afternoon dose of prednisone approached that expected in normal, nonasthmatic subjects. Another study looked at the effect of chronotherapy using inhaled steroids. Pincus et al. (38) evaluated 30 asthmatics and demonstrated that single daily administration of inhaled triamcinolone at 3 PM produced similar improvement in lung

function, bronchial hyperresponsiveness and β -agonist use compared to a standard regimen of triamcinolone given four times daily without any increase in systemic effects. These studies support the idea that chronotherapy should play a role in the judicious use of corticosteroids for nocturnal asthma and that 3 PM is the most effective time of administration.

Evidence suggests that there is also a time dependence to the adverse effects of corticosteroids, since circadian variability exists for risk of adrenal suppression within a 24-hour dosing schedule (7). Maximum inhibition of adrenal gland function occurs with a regimen dosed at the end of the activity cycle and during sleep. Minimum inhibition occurs during the morning and early afternoon. At high enough doses of corticosteroids, the circadian variation in adrenal gland function may be overridden, so that suppression can occur with all regimens.

Although theophylline preparations have generally fallen out of favor for the treatment of asthma, they may be useful in the treatment of nocturnal asthma when administered at specific times in relation to the onset of symptoms. Numerous possible mechanisms of action have been proposed for theophylline, including an anti-inflammatory one. In support of this idea, Jarjour (39) demonstrated that nocturnal administration

of theophylline increased the tolerance to inhaled antigen and diminished the severity of the late asthmatic response. Martin et al. (40) conducted a study involving 16 subjects with nocturnal asthma, randomized to receive either a once-daily preparation of theophylline at dinner-time or conventional twice-daily dosing for 5 days prior to crossover. The single dose regimen resulted in a higher nocturnal serum theophylline concentration and an improved morning FEV₁. The higher daytime serum theophylline level in the conventionally treated group was not associated with an increase in daytime lung function. This study indicated that time-related dosing of theophylline yields superior responses compared to a conventional dosing schedule.

One of the concerns regarding use of theophylline has been its suspected effect on sleep. Martin found no difference in polysomnographic evaluation of his asthmatic population (40) at a higher nighttime serum theophylline concentration. However, an earlier study by Rhind et al. (41) suggested that theophylline may impair sleep quality in asthmatics. The issue is complicated by the fact that, since airway dysfunction itself affects sleep, the secondary effect of theophylline may be difficult to interpret.

Several studies have examined the role of long-acting β -agonists in the treatment of nocturnal asthma. These medications incorporate chronotherapeutic principles into their dosing schedule. Fitzpatrick et al. (42) performed a randomized, double-blind, placebo-controlled crossover study evaluating two different doses of salmeterol (50 and 100 μ g) in 20 patients with nocturnal asthma. Only the 50 μ g dose significantly improved overnight peak expiratory flow and quality of sleep. It is likely that at higher doses, sleep is disrupted due to central nervous system absorption and stimulation. A subsequent investigation by Selby et al. (43) focused on a head-to-head comparison of inhaled salmeterol and oral sustained-release theophylline, using a double-blind, crossover design in 15 patients with nocturnal asthma. There were no major differences detected between the two regimens in terms of symptoms, pulmonary function and side effects. There was a small benefit in sleep quality with salmeterol. The largest study involving long-acting β -agonists enrolled 474 subjects with nocturnal asthma in a randomized, double-blind, placebo-controlled, multicenter clinical trial, to evaluate the effect of inhaled salmeterol on asthma outcomes (44). After 12 weeks of therapy, salmeterol significantly improved lung function (both

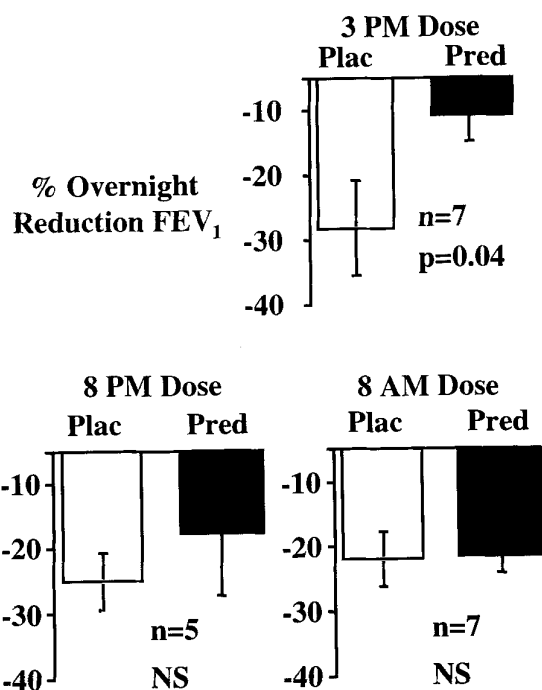


Fig. 6. The effect of the timing of oral corticosteroids on the percent overnight reduction in FEV₁ in subjects with nocturnal asthma. Plac = placebo, Pred = prednisone. Adapted, with permission, from reference 37.

FEV₁ and peak expiratory flow rates), increased the percent of symptom-free days and nights, and decreased supplemental albuterol use.

Wenzel's study on the role of leukotrienes in nocturnal asthma (17) also had a therapeutic arm. Twelve subjects with nocturnal asthma were given zileuton, a 5-lipoxygenase inhibitor, in a randomized, double-blind, placebo-controlled fashion. Zileuton decreased both bronchoalveolar lavage and urinary leukotrienes. Nocturnal FEV₁ also demonstrated a trend toward improvement ($p = 0.086$). These changes were associated with significant reductions in 4 AM eosinophilia (fluid as well as blood). Newer leukotriene-modifying agents such as montelukast are administered at bedtime, with chronotherapeutic strategies in mind.

Since vagal tone is increased at night, anticholinergic therapy is more effective for control of nocturnal asthma symptoms than for daytime symptoms. Availability of longer-acting anticholinergic medications should be particularly helpful in this regard. Use of chronotherapy for agents such as cromolyn and nedocromil is not well understood.

Although there are multiple studies on chronotherapy for the treatment of nocturnal asthma, there are few overall guidelines with respect to when this therapy should be initiated. General strategies should include considering selective timing of a drug as an alternative to increasing its dose or adding another agent to attain control of asthma symptoms. The National Heart, Lung and Blood Institute has stratified asthma severity as mild, moderate and severe (45). The frequency of nocturnal awakenings is included in this characterization. For mild persistent asthma, inhaled corticosteroids dosed in the routine fashion should, over time, reduce airway inflammation and alleviate nocturnal asthma symptoms. Timed dosing may thus be more relevant for the moderate or severe asthmatic. Certainly, whenever an oral corticosteroid is required for an asthma exacerbation in a patient with nocturnal awakenings, there is evidence to support 3 PM administration. Anticholinergic medication should be considered as a nighttime rescue medication for all asthmatics. These and other recommendations for a chronotherapeutic approach to nocturnal asthma are summarized in Table 2.

Indirect therapy for nocturnal asthma is also important. Environmental control measures are essential and should focus on limiting the patient's exposure to allergens. Removal of pets from the bedroom, use of mattress and pillow

TABLE 2
A Chronotherapeutic Approach to Nocturnal Asthma

AM	3 PM	6–7 PM	qHS
LA- agonist	Oral	SR-theophylline corticosteroid	Leukotriene modifier
			LA- agonist Anti-cholinergic

qHS = at bedtime; LA= long-acting; SR = sustained-release.

covers, and carpet-free floors are some examples of helpful changes. Allergic rhinitis most likely demonstrates circadian variability as well (4) and should be treated with anti-inflammatory medications. Finally, since the obstructive sleep apnea syndrome and snoring can increase vagal tone and nocturnal bronchoconstriction, these entities should be diagnosed and treated appropriately. Guilleminault (26) has demonstrated that continuous positive airway pressure in a group of patients with concomitant asthma and obstructive sleep apnea syndrome (OSAS) improved both conditions.

Summary

Nocturnal asthma is defined as an exacerbation of the underlying asthma condition at night, with usual peak flow variability of at least 20%. It is relatively common, affecting approximately two-thirds of asthmatics. The underlying mechanism likely involves endogenous circadian rhythms acting on the hyperreactive bronchi of people with asthma. Sleep seems to have a contributory role. Although patients with more severe asthma often have nighttime symptoms, nocturnal asthma may have some unique features. Circadian activation of inflammatory cells and mediators may occur to a greater degree in these individuals. A chronotherapeutic approach, in which corticosteroids, long-acting β -agonists, slow-release theophylline, leukotriene modifiers and anticholinergic medication are administered at specified times during the day, may enhance response to therapy. An increased understanding of circadian rhythms and their impact on nocturnal asthma should ultimately lead to the development of novel therapeutic strategies.

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