Diurnal Rhythm of Asthma

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A diurnal rhythm in the occurrence and severity of asthma symptoms is almost universal with disturbed sleep due to enhanced symptoms at night paralleled by a change in lung function. The mechanisms involved are not completely understood. However, it appears to be related to an exaggerated response to a circadian rhythm in lung function observed in healthy individuals. The circadian nature of asthma must be considered in diagnosis and evaluating the adequacy of therapy. Inhaled therapy with additional suppressive and anti-inflammatory treatment as required should be effective in treating most patients with nocturnal asthma.

The diurnal rhythm of asthma has often been described and is implicit in reports of sleep disturbed by asthma which date back to antiquity. Maimonides, who was body physician to Saladin, noted this phenomenon in the Saladin’s son, and there are many references to nocturnal asthma from the 17th century onwards. Sir Thomas Willis blamed the heat of the bed as the cause for nocturnal asthma and he advised leaving the bed and sleeping in a chair. By contrast, Maimonides recommended celibacy. One of the earliest references to the diurnal nature of asthma is by Salter in the 19th century, who pointed out that pollen asthma was associated with a diurnal rhythm.

The observation that sleep could be regularly disturbed by asthma suggested a rhythm with a 24-hr cycle and such a circadian rhythm is called diurnal if the trough occurs during the night. The improvement of asthma by day with deterioration at night therefore conforms to a diurnal rhythm. The circadian nature of this condition is well known to both patients and clinicians and has important clinical implications. Other rhythms with a longer period than 24 hours have been described in asthma and the influence of seasonal changes is well known, but the diurnal rhythm is almost universal and explains many clinical features of asthma.

Clinical Features

The diurnal rhythm of asthma helps in diagnosis and also provides valuable information about severity. The diurnal rhythm of symptoms is paralleled by a change in lung function and this can be conveniently and easily measured by peak expiratory flow estimations. Peak flow measured over a 24-hr cycle will show a characteristic circadian rhythm with the peak during the afternoon and the trough in the early hours of the morning. This can be used not only for diagnostic purposes but also to explain why patients may be awakened from their sleep or awake first thing in the morning with symptoms of asthma.

The diurnal rhythm also explains why it may be misleading to estimate asthma severity by measurements made only during the day. Nocturnal symptoms and lung function provide more sensitive information about the severity of asthma as this is when it is worst. Thus, in any assessment of the adequacy of therapy, questions relating to nocturnal events such as sleep disturbance and the use of an inhaler at night provide valuable additional data.

Basic Mechanisms

The diurnal rhythm of lung function which subserves the circadian pattern of asthma appears to be an exaggeration of a normal 24-hr cycle of lung function. Numerous studies of diurnal variation of lung function in healthy subjects have nearly always demonstrated the existence of such a rhythm. This can be shown for complex measurements of lung function, but more readily with simple repetitive ones such as peak expiratory flow measurement. The majority of healthy subjects have a circadian rhythm in peak flow with an acrophase (peak) at about 3:00 to 4:00 pm. The bathyphase is 12 hours later between 3:00 and 4:00 am. The amplitude of the rhythm is between 5 and 10 percent of the mean value, which is at normal levels for healthy individuals.

Asthma patients have a much greater amplitude of diurnal rhythm with the same timing of peak and trough values. The mean peak flow is below predicted and, while this is usually associated with a reduction in both peak and trough values, sometimes this is produced solely by a fall in the overnight peak flow value.

The asthmatic circadian rhythm appears to represent an exaggeration of a healthy rhythm combined with a lower level of lung function. These physiologic observations correlate well with clinical features such as sleep disturbance in patients who are perfectly well during the day, and among those symptomatic by day, a worsening of symptoms at night.

The likelihood that the diurnal rhythm of asthma is an amplification of a healthy diurnal rhythm does not explain how it is caused. A number of factors have been identified which have a temporal association with the circadian variation. However, since they also occur in healthy individuals they are unlikely to be the sole cause of diurnal rhythm.

Epinephrine

It has now been clearly established that there is a circadian variation in plasma epinephrine levels which has a very similar phase to that of the peak flow changes of asthma. This rhythmic change in plasma epinephrine also coincides with changes in plasma cyclic AMP and histamine. Although associated with peak flow changes, the fluctuations in plasma epinephrine are unlikely to be the cause as they are similar in magnitude and phase to those observed in healthy subjects. Fluctuations in plasma cortisol levels also have a diurnal rhythm, but this is found in healthy subjects and is less in phase with the airway rhythm.

Changes in beta receptor numbers have also been examined but these do not account for cyclic variations in peak flow. Beta receptor responsiveness, if anything, is greater during the night than during the day; thus, loss of receptor responsiveness during the night cannot explain the fall in lung function.

Immune Factors

Cyclic variations in immunopathology have also been sought but apparently do not explain the rhythm of asthma which can occur in patients with or without atopy and...
independent of prick test status (ie, in those with intrinsic and extrinsic asthma).

There does not appear to be a significant correlation between the circadian rhythm and the presence or absence of a late phase reaction and therefore it is not possible to explain the nocturnal events simply as manifestations of a type 3 immune response.

Skin and airway reactivity to histamine does have a circadian rhythm with responsiveness being greatest during the night, but this is likely to be a reflection of asthma rather than its cause and is discussed further below.

Posture

Recumbency may cause a small loss of lung function. Such a decline is, however, also found in healthy subjects and does not appear to cause the circadian variation. This conclusion is strengthened by observations that patients with asthma show an improvement in lung function during the day even if they remain recumbent. Variation in lung function is more related to clock hour than to posture.

Acid Reflux

Recumbency may also lead to acid reflux, which has been identified as a potential cause for nocturnal symptoms. Although many patients with asthma have acid reflux, this bears a poor relationship to symptoms and its treatment is usually of little value in managing nocturnal asthma. Acid or gastric reflux also occurs in healthy subjects and therefore can only be regarded as a trigger factor, if it has any relationship to nocturnal asthma at all.

Airway Cooling

Although Sir Thomas Willis thought the heat of a bed caused asthma, there is some evidence that airway cooling at night may occasionally trigger nocturnal asthma. Airways cool with the fall in body temperature during sleep, combined with hyperventilation, may be sufficient to increase airway reactivity and make asthma more likely at night. Some studies have claimed to show that warming and humidifying the inspired air at night prevents these attacks, but this requires further evaluation and cannot provide the sole explanation for nocturnal asthma as airway cooling is a ubiquitous phenomenon and not peculiar to asthmatic patients.

Sleep

Apart from cyclic variations in plasma epinephrine levels, the other factor likely to explain the circadian variation of asthma is sleep itself. Some studies have shown that asthmatic patients working on shifts show a phase change in their diurnal rhythm which suggests that sleep rather than clock hour is determining the pattern of their asthma. This suggests a link between sleep and the circadian rhythm, but on the other hand sleep deprivation or disturbance has a weak and inconsistent effect on the circadian rhythm, which suggests that the link is unlikely to be of great importance and that sleep interruption is not a useful means of therapy. The association between sleep and the clinical variation of asthma is likely to be the result of two basic circadian rhythms with similar phase relationships and entrained by a common factor such as rest, arousal or light/dark cycle.

Airway Reactivity

Factors which are associated with nocturnal asthma, such as the fall in plasma epinephrine and acid reflux, occur in healthy subjects and therefore may be regarded as trigger factors if they play any important role in pathogenesis. This suggests that underlying airway reactivity sets the scene for these normal stimuli. This idea receives support from a number of studies of occupational asthma.

In many patients sensitized to an occupational agent (ie, grain mite), a challenge will not only produce an immediate attack of asthma but successive nights of asthma which continue for many days. Thus, a single challenge will produce a marked diurnal rhythm as seen in spontaneous asthma. This is likely to have resulted from a change in airway reactivity; such a relationship between airway reactivity and diurnal variation has been established. The exaggeration of a healthy circadian variation of asthma may therefore reflect increased airway responsiveness and has no special nocturnal cause.

Possible Mechanism

The basic cause for the circadian variation of asthma has not been established but appears to be related to airway reactivity. Healthy airways show a circadian rhythm which becomes exaggerated in asthma and is usually associated with a decline in lung function. The phase relationship with circulating plasma epinephrine and sleep are likely to be facilitative rather than causal, with factors such as acid reflux or airway cooling acting as a trigger (Table 1).

The management and significance of the diurnal rhythm of asthma is therefore related to the underlying pathogenetic mechanism of asthma itself, such as airway reactivity and mediator release, and these factors require the attention of clinicians rather than a specific nocturnal cause.

Asthma Deaths

As mentioned above, the diurnal rhythm of asthma can account for many of the clinical features such as sleep disturbance and early morning chest tightness. The circadian pattern also means that inquiry about nocturnal events is important to determine the severity of asthma. It is in this context that asthma deaths need to be considered.

The marked diurnal variation in lung function observed in some patients with asthma suggests that they may be particularly at risk during the night because lung function can seriously deteriorate in these patients. The relationship between circadian variability and bronchial reactivity would

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<th>Table 1—Possible Mechanisms Causing Increased Circadian Rhythmicity in Asthma</th>
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<td>Cyclic changes in plasma epinephrine</td>
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also suggest that these patients might be at risk, as airway function is brittle and sudden potentially fatal changes in airway caliber might occur with very little warning.

A number of studies have shown a clustering of asthma deaths at night and, in a survey carried out at the Brompton Hospital, London, the nocturnal timing of respiratory arrest or death was found to occur in patients with a large premorbid circadian variability of peak flow. Patients whose lung function deteriorates markedly at night and who also have very reactive airways, may be at particular risk of sudden death from asthma.

There are a number of other potential causes for fatal asthma, but most surveys of asthma deaths have shown that undertreatment rather than overtreatment is an important contributory factor. This indicates that prompt and effective control of bronchial reactivity and the associated circadian variability in lung function may reduce the risk of sudden death, as well as relieving the morbidity associated with nocturnal asthma. The management of this particular at-risk group is, therefore, the management of the diurnal rhythm.

**The Diurnal Rhythm of Asthma**

The management of the asthmatic diurnal rhythm is the management of asthma itself as this rhythm is a function of bronchial reactivity and whatever triggers asthma. The events at night are thus a consequence of a 24-hr cycle and therefore do not require timed nocturnal therapy, but rather treatment over the full 24 hours. Patients with asthma usually display a below-normal level of lung function with a much larger amplitude of circadian variation; both factors may be important in management. Elevation of mean lung function may help relieve nocturnal symptoms purely by virtue of raising the evening values such that the overnight fall is insufficient to wake the patient. Better and more comprehensive treatment would not only raise the mean level of lung function, but also reduce the diurnal amplitude. The effect would be to limit the overnight fall which would further protect the patient both from symptoms and the risk of sudden death.

Therapy of circadian rhythm would depend, in part, on the severity of asthma as reflected by the mean level of lung function as well as the overnight fall. Nocturnal features of asthma may often be largely of a bronchitic nature. Thus, patients who complain of nocturnal cough, if attributed to asthma, should also be managed in a similar manner. The majority of patients with nocturnal bronchitis will also show deterioration in lung function, but sometimes this is trivial in comparison to those other patients who have marked falls in lung function without bronchitis and in whom dyspnea and chest tightness is the major clinical feature. As with asthma therapy, removal of precipitating factors may reduce the circadian rhythm but this takes some time and only rarely provides successful treatment. For the majority, drug therapy is required.

**Bronchodilator Therapy**

The diurnal rhythm can be successfully treated with bronchodilator therapy in many patients. In relatively mild asthma, minor nocturnal symptoms may be the predominant clinical feature and it is tempting to treat such patients as if they have episodic asthma and only relate bronchodilator treatment to the attack. Under these circumstances, bronchodilator medication is usually given before retiring to bed in the hope that this will prevent symptoms. This strategy often works but ignores the 24-hr cycle which has determined the nocturnal event. Better results may be achieved by giving treatment in the morning as well as the evening so as to raise the daytime lung function and produce a more sustained treatment of the underlying bronchial reactivity and inflammation.

There is considerable debate as to the most effective bronchodilating agent for treating the diurnal rhythm as well as the best route of administration. Inhaled therapy has an advantage over oral treatment as it minimizes risks of adverse side effects; these side effects can be a particular problem with theophylline therapy. On the other hand, inhaled beta agonist treatment in conventional doses may not last as long as sustained oral formulations.

I personally prefer inhaled therapy because of its wider safety margin and find that by increasing the dose and by using treatment at least bid, many patients can respond adequately to this treatment and do not require oral therapy. Others are equally satisfied with the effects of sustained release oral preparations, either of beta agonist or theophylline, and argue that if properly supervised, systemic side effects are not a major problem. However, proper supervision of oral therapy remains a major practical problem and reports of theophylline toxicity point to the difficulties encountered with such treatment, particularly in the elderly patient.

A relatively unexplored area of bronchodilator management is the clinical observation that some patients respond to one agent significantly better than another. It may be best not to be too doctrinaire, and to use the bronchodilator or alternative route of administration the patient is more happy with.
treatment, particularly in childhood asthma and in the presence of atopy. The mode of action is unclear, but this treatment has a good safety record and should always be considered when patients are not responding to bronchodilator therapy and have a marked circadian rhythm. There have been few studies looking specifically at the role of sodium cromoglycate in the control of the diurnal rhythm of lung function, but symptomatic relief can be achieved in terms of sleep disturbance and nocturnal use of bronchodilators.

More potent suppressive and anti-inflammatory therapy can usually be achieved with corticosteroid therapy. Oral administration carries the risk of adverse side effects and for this reason inhaled steroid treatment is usually preferred if required on a long-term basis.

Over the last decade or so, inhaled steroid therapy has proven its worth in the management of asthma, being effective and free from adverse systemic side effects. It is, therefore, an effective substitute for oral steroid therapy, and in patients not responding to bronchodilator therapy it can effectively control symptoms.

There is some debate as to the effectiveness of steroid therapy in controlling the circadian variation of asthma. Undoubtedly some patients with marked diurnal variation show little or no response to corticosteroid therapy even when given orally in high doses. On the other hand, these patients are often intractable to the full range of treatment and probably represent an unusual subset of asthma. The majority of patients with chronic asthma respond well to corticosteroid therapy and that response includes an improvement in nocturnal symptoms. Inhaled steroid therapy can be shown to reduce the circadian variation and improve control of nocturnal symptoms both by raising mean levels of lung function and also by reducing the amplitude of the rhythm (Fig 1).

Inhaled steroid therapy also has merit in providing specific topical anti-inflammatory therapy and this treatment, when given in combination with bronchodilators, means that a comprehensive attack on the underlying pathogenesis of asthma can be achieved. In view of the growing appreciation of the importance of inflammation in asthma pathogenesis, the merits of inhaled steroid therapy are such that its role needs to be re-evaluated. Freedom from adverse side effects and an anti-inflammatory role suggests that inhaled steroid therapy should be used more frequently than oral steroids have been employed in the past, and should be regarded as a therapeutic competitor when considering how best to control asthma in patients for whom inhaled bronchodilator therapy is insufficient. This puts inhaled steroids as an option to be considered in competition with sodium cromoglycate and additional bronchodilator treatment.

Chronotherapy

The timing of treatment may be important. Evening doses of bronchodilator may control mild nocturnal asthma and reduce side effects of methyl xanthine therapy. Corticosteroid therapy may be effective when given on alternate days and this may minimize adverse side effects. Oral steroid therapy taken during the morning or on waking may also have a better therapeutic effect on the diurnal rhythm, as well as producing less adrenal suppression. The importance of asthma chronotherapy has only recently been appreciated by clinicians and much more research is required.

CONCLUSION

Treatment of the circadian rhythm of asthma is treatment of asthma itself and relies on the use of appropriate pharmacologic measures to control underlying bronchial reactivity as well as the inflammatory component and airway smooth muscle constriction. Allergen avoidance may reduce the circadian variation by improving airway reactivity, but the majority of patients require drug therapy. This can usually be achieved with bronchodilator therapy. The judicious use of inhaled therapy, employing additional suppressive and anti-inflammatory treatment as required, should enable the majority of patients with nocturnal asthma to be effectively treated and their underlying diurnal rhythm restored to normal.

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F.B. Brompton Hospital

700 -
600 -
500 -
400 -
300 -
200 -
100 -
0 -

no treatment
inhaled beta agonists
+inhaled steroids

Peak flow
l/min

FIGURE 1. Schematic representation of response to treatment in a patient. Note the rise in mean peak flow and the reduction in amplitude of the diurnal rhythm. Also note the effect of inhaled beta agonist alone and in combination with inhaled steroids.

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Behaviors Factors in the Etiology of Asthma

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Evidence for the role of behavior in the etiology of asthma is reviewed here. Behavioral factors have not convincingly been shown to play a part in the inception of asthma. It has been suggested that asthma attacks can be precipitated by conditioning. Previous experiences leading to the expectation that an attack may occur can be regarded as a behavioral factor which may trigger an attack, possibly by inducing hyperventilation. Further research should focus on the possible role of behavioral factors in maintaining a state of hyperreactivity of the bronchi and psycho-immunologic aspects such as brain-controlled neuroendocrine immune mechanisms.

In considering asthma, the term “etiology” has been often misunderstood. A multiplicity of factors are capable of provoking attacks of asthma, but it is by no means clear what role they play in its pathogenesis. Confusion in the literature stems from the all-too-frequent assumption that factors which provoke asthma attacks also cause the condition itself. It is extremely important to clarify what is understood by the term as it applies to asthma. There are three separate, though interrelated, aspects of the etiology of asthma. Inception is the period when the bronchi first develop the capacity to undergo narrowing response to various provocative factors. Next occurs maintenance and reinforcement of this state of hyperreactivity. Third, hyperreactive bronchi are provoked, giving rise to clinically recognizable attacks of asthma.

The role that behavioral factors may play in the etiology of asthma has to be analyzed in the light of these distinctions. Behavioral factors cannot be considered to be the same as psychologic factors, although often it is impossible to make a clear distinction between them. Behavior can be recognized as a response to a determined stimulus. But in this context, patterns of asthma behavior could be due either to inherent psychologic factors associated with a distinctive type of personality, or they might be secondary to the limitations imposed by asthma on a normal life style.

Behavior and the Initiation of Asthma

Supporters of the psychosomatic theory of asthma have made great efforts to prove that the personality and resulting behavioral patterns of individuals with certain bodily diseases are causally related and very specific to them. Several points of criticism can be raised against these conclusions. Much of the information is subjective or has come from studies in which a considerable bias arose due to the selection of patients who sought medical or psychiatric care. Hence, such patients may have been far from representative of the general asthma population. As has been pointed out by Menges, this “distortion due to selection” could have a profound influence upon the results of psychometric testing. Furthermore, since pre-asthmatic personality features and behavior patterns could not be ascertained, the findings made after the development of asthma may very well have been secondary to the disease.

Some studies have avoided these methodologic shortcomings by, for example, comparing psychologic characteristics of asthmatic patients with those of normal healthy subjects. They revealed no significant personality traits in either adults or children with asthma. In 1979, Creer concluded from a comprehensive review of the literature that it was justifiable to denounce even the slightest suggestion that personality profiles or psychodynamic conflicts may induce asthma. A growing number of psychologists and psychiatrists disagree that there is a causal relationship between an “asthmatic personality,” or a specific emotional conflict, and the inception of the disease (a comprehensive review is given by Kaptein). On the basis of controlled observations it would suggest that psychologic abnormalities and resulting patterns of behavior are rather a byproduct and unrelated to the inception of asthma.

Maintenance and Reinforcement of Asthma

The factors implementing the maintenance or periodic reinforcement of airway hyperreactivity are obscure. It is conceivable that repetitive exposure to some factors provoking asthma attacks might enhance increased bronchial hyperreactivity. In this context the maintenance and reinforcement of hyperreactivity appears to be closely related to provocative agents.

Cohen and Lask argued that, on the basis of a pathophysiologic substrate, any form of emotional arousal may trigger asthma attacks. Obviously, there are emotional reactions to an asthma attack such as anxiety, fear of death, or increased dependence on others. For instance, initially, asthmatic attacks may be provoked by allergy, or recurrent infections, but later, emotional factors may become predominant in provoking attacks of asthma.

Based on the principle that behavior is learned, it has been suggested that this occurrence of asthma attacks can be precipitated by conditioning. Clinicians recognize a situation where a subject who knows that a particular flower has caused attacks previously will develop such an attack merely by seeing a paper imitation of the flower. A pattern of behav-