Nocturnal asthma: mechanisms and treatment

Patients with asthma often wheeze at night and in the early morning. This symptom may prove difficult to treat,^{1 2} but it is important: sudden death in asthma tends to occur at these times.³⁻⁵ Three hundred years ago Dr Thomas Willis believed that nocturnal wheezing was due to overheating of the blood by the bedclothes.⁶ Since then many other possible explanations have been considered, but now the underlying mechanisms are being elucidated.

In the past advice on treatment was often based on belief that nocturnal wheeziness was due to exposure to allergens in bedding such as house dust and feathers—yet avoidance of these allergens provided no benefit.⁷ More rigorous exclusion of house dust mites does, however, improve early morning wheeze,⁸ and experimental inhalation of allergens may cause wheezing on several subsequent nights.⁹ This indicates that exposure to allergens—and particularly the late reaction—may contribute to nocturnal asthma. On the other hand, patients with intrinsic asthma (in whom there are no allergic factors) also have nocturnal wheezing.² The relation between nocturnal asthma and sleep is uncertain, and studies of interruption and deprivation of sleep show that bronchoconstriction may occur at night independently of sleep.¹⁰ Considerable fluctuations in airway resistance are reported in normal people during rapid eye movement sleep,¹¹ but there is no clear relation between the stage of sleep and awakening with wheeze.^{12 13} Studies of bronchomotor tone during undisturbed sleep in asthmatics are needed.

Interruption of treatment with bronchodilators is not the primary cause of nocturnal asthma, since wheezing at night persists even when treatment is spaced regularly over 24 hours¹⁴—and the phenomenon is present in untreated patients. Acid reflux into the oesophagus while lying down might initiate reflex bronchoconstriction,¹⁵ but the timing of nocturnal bronchoconstriction is against this hypothesis, and wheezing is unrelated to the supine posture. Mucociliary clearance is impaired in normal people during sleep,¹⁶ and retention of mucus might therefore contribute to narrowing of the airways at night—but it is unlikely to be a large component of bronchoconstriction, since wheezing is rapidly relieved by inhaled β agonists.

Cooling of the upper airways may cause bronchoconstriction in asthmatics, and the fall in body temperature at night might

therefore initiate bronchospasm. Though the fall in core temperature at night is small, breathing warm humidified air at night does appear to reduce nocturnal wheeze.¹⁷ The tone of the airways is regulated by the autonomic nervous system, and abnormalities in autonomic control have been described in asthma, so a change in autonomic responsiveness of the airway at night might underlie nocturnal asthma.¹⁸ Bronchodilator responses to inhaled or infused adrenaline are not reduced at night, however, suggesting that impaired β adrenoceptor function plays no part in nocturnal asthma.¹⁹ Though some of these proposed mechanisms might account for exacerbations of asthma at night in some patients, they do not provide a universal explanation for nocturnal asthma.

Recently, however, both our understanding and analysis of circadian biological rhythms have improved, and the evidence now suggests that they may underlie nocturnal asthma.^{20 21} A small but detectable diurnal variation in bronchomotor tone is found in normal people²²: the diurnal rhythm in peak expiratory flow has a mean amplitude of 8%. Asthmatics have a similar circadian pattern, but with an amplitude of 50%, implying that nocturnal asthma represents an exaggeration of the normal rhythm in bronchial tone.²³ Asthmatic airways are hyperreactive to many constrictor stimuli, and nocturnal asthma is probably simply a manifestation of bronchial hyperreactivity. Indeed, there is a correlation between the degree of bronchial hyperresponsiveness to inhaled histamine and the amplitude of the diurnal variation in peak flow.²⁴ So nocturnal asthma seems to be due to the factors responsible for the diurnal change in bronchomotor tone in normal people, with the changes in tone exaggerated because of bronchial hyperreactivity.

Several of the circadian rhythms may be relevant. The circadian variation in plasma cortisol concentration has long been recognised, and steroids are effective in treating asthma. But the fall in plasma cortisol value at night occurs several hours before maximal bronchoconstriction,²⁵ and an infusion of hydrocortisone at a dosage which abolishes the nocturnal fall in plasma cortisol fails to prevent nocturnal asthma.²⁶ The actions of cortisol are delayed, however, and the effect of withdrawal of endogenous steroids at night might possibly contribute to nocturnal wheeze. Endogenous plasma adrenaline is important in asthmatic patients as a defence against broncho-

constriction.²⁷ The fall in peak flow at night is closely correlated with a reduction in urinary catecholamine excretion²⁸ and with a fall in plasma concentrations of adrenaline, the lowest of which occur at 0400 hours—the time of maximal bronchoconstriction.²⁵ This fall in plasma adrenaline at night is due to reduced secretion from the adrenal medulla, since there is no diurnal change in adrenaline clearance.²⁷ Secretion of adrenaline is regulated by the hypothalamus, an area closely concerned in the central control of circadian rhythms.²⁹

The fall in plasma concentrations of adrenaline at night in asthmatics is identical with that seen in normal people, but withdrawal of the protective effect of adrenaline may affect bronchial tone to an important degree only in asthmatics. An analogy may be drawn with the effect of a β blocker (such as propranolol) in producing bronchoconstriction in asthmatic but not normal people—presumably by blocking the effects of endogenous adrenaline on airway β receptors.³⁰ Adrenaline may bronchodilate not only by a direct effect on airway smooth muscle β receptors in the airways but also by stimulating β receptors on pulmonary mast cells; these inhibit the secretion of bronchoconstrictor mediators such as histamine and leucotrienes.³⁰ Thus withdrawal of endogenous adrenaline at night may increase the release of mast cell mediators. Indirect evidence for this is provided by an increase in plasma histamine at night in asthmatic but not normal people which correlates with the fall in adrenaline and peak flow.²⁵ Infusion of adrenaline in low concentration at night reduces the raised plasma concentration of histamine towards normal.²⁵

Stimulation of the vagus nerve causes bronchoconstriction, and vagal tone might possibly increase at night. Mediators such as histamine might possibly stimulate irritant receptors in the airway to produce bronchoconstriction by vagal reflex.¹⁸ The fall in plasma concentrations of adrenaline might increase vagal tone.³⁰ As long ago as 1698 Dr John Floyer, himself a sufferer of nocturnal asthma, suggested that wheezing occurred at night “when nerves are filled with windy spirits.”³¹ No direct measurements of vagal tone in the airways at night have been possible, but changes in heart rate and in sinus arrhythmia at night may reflect increased vagal tone,³¹ and there is an association between heart rate and nocturnal bronchoconstriction.¹⁹

Probably, then, nocturnal asthma may be explained by a coincidence of several rhythms: a fall in circulating adrenaline, the delayed effects of steroid withdrawal, and increased vagal cholinergic tone. These factors lead to small changes in the tone of the airways in normal people but to bronchoconstriction in asthmatics because of exaggeration by hyperreactivity and possibly by increased release of mediators.

The treatment of nocturnal asthma may be surprisingly difficult. Since bronchial hyperreactivity seems to be the amplifying mechanism the logical first step is to improve control of the asthma. Strict avoidance of allergens may improve nocturnal asthma,⁸ but such extreme measures are rarely practicable. Nor is manipulation of the central clock underlying circadian rhythms likely to be a useful approach. In many cases regular treatment with inhaled β_2 agonists and steroids improves nocturnal symptoms, but in some patients nocturnal asthma proves difficult to treat even when asthma may be adequately controlled during the day. Giving a bronchodilator which lasts overnight is a logical approach, but slow release oral preparations of β_2 agonists have not proved to be very effective.³² Slow release preparations of theophylline given in a single dose at night produce steady plasma concentrations within the therapeutic range over 10 hours, and these seem to be the most effective treatment.³³ Side effects are not usually a problem at night. Finally, since the mechanism of

nocturnal asthma is multifactorial, a combination of different treatments seems logical in difficult cases.

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