CHAPTER 1.1

EPIDEMIOLOGY AND THE CONCEPT OF UNDERLYING MECHANISMS OF NOCTURNAL ASTHMA

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Respir Med 1993; 87 (suppl B): 37-39
Abstract

Nocturnal symptoms are common in asthma, even when patients are regularly seen at an outpatient clinic. Inflammation is generally accepted as a general feature of asthma and the severity of this basic inflammatory process can be increased by exogenous triggers such as exposure to allergens and non-allergic stimuli. Superimposed endogenous circadian rhythms may play a more important and intricate role in the circadian modulation of the inflammatory process by changing the number of cells, their release of mediators and/or the susceptibility of airway smooth muscle and vasculature. For instance, an increase in vagal tone may induce nocturnal bronchoconstriction which is further enhanced by falling catecholamine levels. Together, the reduced nocturnal catecholamine levels and the diminished bronchodilating capacity of the NANC system and the low cortisol levels oppose possible protection against inflammatory processes leading to nocturnal airflow obstruction.

Introduction

Nocturnal symptoms of dyspnoea and wheezing are common in asthmatic patients and are thought to be related to the severity of the disease (1). Both in healthy subjects and asthmatic patients a circadian variation in airway diameter exists, with best lung function values during the day and worst values at night. In healthy subjects differences between daytime and nighttime values are small, in asthmatic patients they may be large with the consequence of nocturnal airflow limitation and symptoms such as cough, wheeze, dyspnoea and waking up. Although nocturnal complaints of asthma have been recognized for a long time, little is known about its epidemiology. The mechanisms that contribute to the amplified 24 hours swings in pulmonary function are not yet fully clear but the concept is growing. In this article we will focus on both epidemiology and pathophysiology and try to come to a concept of mechanisms that play a role in nocturnal asthma.

Epidemiology

Throughout history the occurrence of nocturnal complaints of asthma have been reported (2).

In 1973 the first epidemiological study on the prevalence of nocturnal asthma appeared and was repeated in 1988. Turner-Warwick showed in 1988 that 39% of a non-hospital-based population in the United Kingdom woke up every night, 64% woke up at least 3 nights per week and 74% woke up at least 1 night per week (3).
These data were comparable to those of the study 15 yrs earlier, and the author concluded that not much had changed despite the introduction of inhaled corticosteroids. In 1991 we studied the epidemiology of nocturnal complaints and early morning dyspnoea in 796 asthmatic children from our own outpatient clinic. The questionnaire referred to the last 3 weeks before a regular control visit. Forty seven percent reported nocturnal complaints or early morning dyspnoea. Only 6% reported to have complaints every night. In our population as well as in the study population from the United Kingdom about half of the patients used inhaled corticosteroids, drugs known to reduce the 24 hour amplitude of the lung function. The difference in results between the two studies may be explained by differences in age of the study populations and probably differences in frequency of medical control, since the population studied by Turner-Warwick was only defined as patients for whom an inhaled bronchodilator was prescribed by a general physician. Despite differences in outcome of the two studies, we have to conclude that nocturnal symptoms of asthma are still common in the nineties even in a regularly controlled asthmatic population.

Mechanisms

Both exogenous triggers, and probably more important, circadian variations in endogenous mechanisms, such as bronchial responsiveness, the autonomic central nervous system and cortisol secretion, modulate the inflammatory processes in the airways underlying the asthmatic expression. This may ultimately result in variation of the airway diameter over 24 hours.

BRONCHIAL RESPONSIVENESS

The increase in airflow obstruction during the night was thought to be a consequence of the increase in bronchial responsiveness that was observed at the same time (4). However, in asthmatic children we found that the circadian variation in bronchial responsiveness can be independent of the degree of airflow obstruction (5) as confirmed by Bonnet et al. (6). This indicates that an increase in bronchial responsiveness overnight in itself is not responsible for nocturnal airflow obstruction and that other factors are involved.

CORTISOL

Corticosteroids are well-known for their beneficial effect in restoring pulmonary function in severe asthma attacks with a latency of several hours. The circadian variation in serum cortisol shows trough levels at 01.00 h and peak levels about 08.00 h. Postma et al. (7) observed levels of serum cortisol in patients with chronic obstructive pulmonary disease (COPD) comparable to those in the matched healthy
controls. Together with the observation that infusion of cortisol did not prevent the nocturnal fall in pulmonary function in five out of six patients (8) has led to the believe that the fall in cortisol during the early night is not in itself responsible for the decrease in airway diameter at 04.00 h.

THE AUTONOMIC NERVOUS SYSTEM
The circadian variation in airway diameter is known to be under control of various components of the autonomic nervous system such as the parasympathetic system, β-adrenergic sympathetic system and the non-adrenergic non-cholinergic (NANC) system.

The parasympathetic system
Increased parasympathetic tone causes a decrease in the airway diameter. In adult patients with asthma and in patients with COPD an increase in parasympathetic activity was observed during the night (9,10). We were unable to confirm this finding in children with nocturnal asthma (11). Moreover, after heart-lung transplantation, when vagal innervation is lost, a circadian variation in airway diameter is still present (12). These observations indicate that parasympathetic activity contributes, but does not fully explain nocturnal airflow obstruction.

The β-adrenergic system
The β-adrenergic system is of importance for airway dilatation and consists of circulating catecholamines and β-receptors on cell membranes of inflammatory cells, cholinergic ganglia and airway smooth muscle. Circulating catecholamines such as adrenaline and noradrenaline show a circadian variation with lowest levels at 04.00 h coinciding with the nocturnal increase in airflow obstruction. β2-receptor density on peripheral blood cells is also lowest during the night. These observations suggest that the diminished bronchodilating capacity during the night is responsible for the nocturnal increase in airflow obstruction. However, correction of the nocturnal dip in serum adrenaline by infusion of adrenaline did not prevent the fall in pulmonary function (10). Moreover, we did not observe differences in adrenaline and noradrenaline urinary excretion between asthmatic children with and without increased nocturnal airflow obstruction and their healthy controls (13). This indicates that a fall in circulating catecholamines during the night does not have a direct action on bronchial smooth muscle tone. This fall will provide a smaller protective effect on for instance mast cells, thereby inducing histamine and other mediator release (13). Furthermore, increasing vagal tone can be opposed by inhibition of cholinergic neurotransmission at the level of parasympathetic ganglia and may permit an increase in microvascular leakage, ultimately leading to an increase in airflow obstruction.

The non-adrenergic non-cholinergic system
A circadian variation in NANC neurotransmission has been found as well: a decreased bronchodilator response upon stimulation with capsaicin was found at 04.00 h as compared to 16.00 h in healthy subjects and in asthmatics (14). This decreased bronchodilator response in the morning may result from central modulation of the stimulus or from inhibition of the efferent activity. The authors concluded that nocturnal airflow obstruction in asthmatic subjects may be partly caused by a decreased NANC bronchodilatation.

**Concept of mechanisms in nocturnal asthma**

It is generally accepted that a specific inflammatory process underlies the pathogenesis of asthma. That an inflammatory process may play a role in nocturnal asthma is supported by the observation that anti-inflammatory drugs such as inhaled corticosteroids reduce the overnight fall in pulmonary function (15). Martin et al. (13) showed, at least in some, but certainly not in all patients with nocturnal asthma an increase in numbers of eosinophils and neutrophils in the nocturnal bronchoalveolar lavage (BAL) fluid as compared to daytime numbers. Jarjour et al. (16) did not observe day-night variations in inflammatory cells in the BAL fluid. Lungbiopsies will probably provide an answer whether an influx and activation of inflammatory cells in the lungs overnight are responsible for the fall in pulmonary function.

At this time we hypothesize the inflammatory process to be a general feature in asthma. The severity of this basic inflammatory process can be increased by exogenous triggers, such as exposure to allergens and non-allergic stimuli. Superimposed endogenous circadian rhythms may play a more important and intricate role in the circadian modulation of the inflammatory process by changing number of cells, their release of mediators and/or the susceptibility of airway smooth muscles and vasculature. Increased vagal tone may induce nocturnal bronchoconstriction. Falling catecholamine levels overnight may induce further decrease of the airway diameter. Together with the reduced nocturnal catecholamine levels, diminished bronchodilating capacity of the NANC system and low cortisol levels oppose possible protection against inflammatory processes, leading to nocturnal airflow obstruction.

**Acknowledgement**

The authors thank dr DS Postma for critically reviewing this manuscript.
References


CHAPTER 1.2

AIMS OF THE THESIS
In this thesis several exogenous factors that may influence the severity of nocturnal airflow limitation in asthmatic children are investigated. Next to the influence of these exogenous factors we investigated the frequency of nocturnal symptoms on our pediatric asthma outpatient clinic.

In Chapter 1.1 a concept of possible mechanisms and interactions between endogenous and exogenous factors that may underly nocturnal airflow limitation is discussed.

In Chapter 2 we investigated the frequency of nocturnal symptoms such as coughing, wheezing, shortness of breath and dyspnea on awakening in the morning in our asthmatic outpatient clinic in children with asthma.

In Chapter 3 a study is presented in which we investigated whether house dust mite exposure levels in houses of asthmatic children are higher than in houses of healthy controls.

In Chapter 4 a study is presented in which we investigated the wheter exogenous factors such as environmental tobacco smoke, the presence of pets, and the levels of house dust mite in houses of asthmatic children with a mono-allergy to house dust mite contributed to an increased circadian peak expiratory flow amplitude.

In Chapter 5 a study is presented in which we investigated whether the seasonal variations in house dust mite exposure contributed to an increase in circadian peak expiratory flow amplitude in asthmatic children with a mono-allergy to house dust mite.

In Chapter 6 we discussed that mite-specific IgE could not be used as an alternative for house dust mite exposure in answer to a study in which the authors suggested that that this could be done.

In Chapter 7 a study is presented in which we investigated in asthmatic children who were already treated with inhaled corticosteroids whether 16 weeks of treatment with the long acting β-adrenergic drug salmeterol leads to a sustained bronchodilator effect and decreased bronchial responsiveness during the day and night. Furthermore, we assessed whether cessation of salmeterol after 4 months, when added to a regime with inhaled corticosteroids, leads to a rebound increase in bronchial responsiveness.

In Chapter 8 a study is presented in which we investigated daytime and nighttime inflammatory parameters in healthy children and in asthmatic children treated with inhaled corticosteroids. Moreover, we assessed whether differences in inflammation
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between healthy and asthmatic children are associated with lung function parameters and whether long-term treatment with salmeterol influenced inflammatory parameters.