Epidemiology and exogenous factors in nocturnal airflow limitation in children
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CHAPTER 9

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS
Nocturnal respiratory symptoms are common in children with asthma. This is generally attributed to increased airway obstruction and hyperresponsiveness at night. A circadian variation in airway diameter has been described both in healthy children and in children with asthma. In healthy children this 24 hours variation is small, and it is enhanced in many asthmatic patients, especially when in an unstable phase of the disease. The best lung function values occur during the daytime, while trough values are generally measured at the end of the night. This causes patients and their parents to wake up with negative consequences for school performance and disruption of family life.

Nocturnal complaints of asthma have been recognized for a long time. An increased nocturnal airflow limitation has already been described in the fourth century AD. In the forties and fifties of this century, research into determinants of increased airway obstruction began, to which the Groningen group contributed. Up to now, research on the phenomenon of nocturnal airflow limitation has largely focussed on endogenous rhythms, such as the contribution of variations of the autonomic nervous system, variations in cortisol secretion, or associations of variations in inflammatory variables and the nocturnal fall in lung function. Although parts of the puzzle have been elucidated, other parts are still unknown. During earlier studies in allergic asthmatic children we have observed that the nocturnal airflow limitation as measured at home improved during a short stay in hospital. This led to the hypothesis that next to endogenous factors, exogenous (environmental) triggers such as allergens and tobacco smoke were also able to modulate the circadian variation in airflow limitation.

This thesis aimed to give more insight in, on one hand, the epidemiology of nocturnal respiratory symptoms in children with asthma who are regularly controlled on an outpatient clinic for asthmatic children. On the other hand, it tries to answer the question whether environmental triggers are of importance for the magnitude of the circadian variation in airflow limitation. As it has been suggested that the inflammatory process in the lungs is more active during the night, environmental triggers, such as inhaled allergens, could activate this inflammatory process. Several studies suggested that the inflammatory process is more severe during the night in patients with nocturnal airflow limitation. These studies show an increase of inflammatory cells and mediators in blood and urine during the night (1-4). More direct evidence is shown by an increase in inflammatory cells and activation markers in bronchoalveolar lavage fluid obtained during the night (5,6). Anti-inflammatory drugs such as inhaled corticosteroids (ICS) are known to reduce the degree of inflammation and reduce 24 hours variation in peak expiratory flow (PEF) (7,8).

Long-acting β2-agonists have proven to be especially beneficial to overcome the nocturnal fall in lung function in asthmatic patients (9). In the earliest studies it has been suggested that they possessed also anti-inflammatory properties, since a single inhalation prevented not only the early asthmatic reaction after allergen inhalation,
but also the late asthmatic reaction (10). Therefore, we studied the effect of 16 weeks treatment with the long-acting β₂-agonist salmeterol on daytime and nighttime lung function, bronchial responsiveness and inflammatory variables in peripheral blood of allergic children treated with ICS.

Chapter 1.1 contains a literature study on the epidemiology of nocturnal symptoms of asthma in different populations. Furthermore, the literature on mechanisms that may modulate the circadian variation in lung function is discussed. It is generally accepted that inflammation of the airways underlies the pathogenesis of asthma. The 24 hours variation in endogenous rhythms such as bronchial responsiveness, the autonomic central nervous system and cortisol secretion modulate the inflammatory processes in the airways, resulting in variation of the airway diameter over 24 hours. In our concept of nocturnal airflow limitation in asthmatic children we hypothesize that the severity of this basic inflammatory process may be enhanced by exogenous triggers, such as exposure to allergens and non-allergic triggers, resulting in larger circadian swings in lung function.

In Chapter 2 we describe a study in which we investigated the frequency of nocturnal symptoms such as cough, wheeze, shortness of breath, and dyspnea on awakening in the morning in 796 consecutive children with asthma attending our outpatient clinic. Nocturnal symptoms were reported in 47% of the children; 6% every night and 34% at least once a week. Only 38% of these 47% with nocturnal symptoms reported these spontaneously. Patients with nocturnal symptoms had a lower FEV₁, perceived their asthma as more severe, and had their daytime activities more affected than those without nocturnal symptoms. FEV₁ seemed to be a poor predictor for nocturnal symptoms. These results confirm that nocturnal symptoms of asthma reflect a more severe disease state. Furthermore it shows that doctors should specifically ask about nocturnal symptoms as they are not spontaneously mentioned. This offers the possibility to introduce appropriate treatment.

In Chapter 3 we have tried to answer the question whether house dust mite (HDM) exposure levels in living and bedrooms of 25 asthmatic children are higher than in those of age and sex matched healthy children, living in the same area. HDM allergen (HDMA) concentrations were not significantly different between the two groups, although a higher cleaning frequency, and more smooth floor coverings were reported in the asthmatic group. We observed that low HDMA concentrations were a general finding in Dutch dwellings in the present generation of children. Smooth floor coverings contained less fine dust and lower concentrations of HDMA than carpeted floors. The large interindividual variation in HDMA concentrations in the different houses suggests an individual approach with regard to environmental measures.
Chapter 4 contains a study in which we investigated in 55 asthmatic children with a mono-allergy to HDM the contribution of exogenous triggers, such as environmental tobacco smoke, the presence of pets, and levels of HDMA in living rooms, bedrooms, mattresses (n=25) and classrooms to an increased circadian PEF amplitude (PEF value every 4 hours during 24 hours expressed as highest minus lowest value expressed as a percentage of the day’s mean value). All children were well controlled with daily ICS. To investigate the influence of these triggers on the circadian PEF amplitude, ICS were withdrawn for 6 days. We found that exposure to environmental tobacco smoke, the presence of pets and high exposure to HDMA concentrations in bedding contributed independently to a higher PEF amplitude after withdrawal of ICS. Highest HDMA exposure sources were mattresses and carpets on a smooth floor.

In Chapter 5 a study is presented assessing whether a seasonal difference in HDMA exposure contributed to an increase in circadian PEF amplitude in 25 asthmatic children with a mono-allergy to HDM. In all children HDMA were collected in living rooms, bedrooms and from the surface of mattresses by vacuum cleaning. In both spring and autumn, PEF amplitude was measured before and 6 days after withdrawal of ICS. This cross-sectional study showed that a higher PEF amplitude was not significantly associated with higher HDMA exposure in mattresses. However, the change in HDMA exposure over seasons (autumn value minus spring value) contributed significantly to the change in PEF amplitude after withdrawal of ICS.

The results of both studies in chapter 4 and 5 strongly suggest that superimposed exogenous triggers enhance the magnitude of the circadian variation in airway diameter next to endogenous modulation.

Chapter 6 is a letter to the editor in answer to a study of De Lovinfosse et al. published in Allergy 1994; 49: 64-66 in which the authors showed a correlation between HDM specific IgE and HDMA exposure levels and suggested that mite specific IgE could be used as a surrogate for mite exposure. In 25 asthmatic children with an isolated allergy to HDM we tried to correlate the same variables (serum mite specific IgE and HDMA levels collected from mattresses). We did not observe a correlation and we could not confirm their statement. This seems logical since the immunological ability of an individual to react to a certain amount of HDM is a probably more relevant factor that may influence IgE production.

In Chapter 7 we present results of a study in forty asthmatic children who were already on daily ICS and randomly treated for 16 weeks with the long-acting β₂-agonist salmeterol or placebo. The effects on FEV₁ and bronchial responsiveness both during the day and overnight were investigated. Furthermore, we assessed whether cessation of salmeterol after 4 months led to a rebound increase in
bronchial responsiveness. We observed in the salmeterol group a sustained higher FEV$_1$ and an improved circadian variation in airway diameter than in the placebo group from 1 to 16 weeks of treatment. Overall mean PC$_{20}$ methacholine from 1 to 16 weeks of treatment was not significantly different between the salmeterol and placebo groups. This lack of improvement in PC$_{20}$ in the salmeterol group could not be explained by a ceiling effect since all children had moderate to severe bronchial responsiveness and all children had enough room for improvement. Cessation of salmeterol after 16 weeks of treatment did not lead to a rebound increase in bronchial responsiveness.

In Chapter 8 we present another aspect of this same study and investigated whether addition of salmeterol to treatment with ICS leads to a beneficial effect on inflammatory variables in peripheral blood during the day as well as overnight. Blood was collected from the same children in the same study as mentioned in chapter 7. Besides this question, we investigated whether a difference in these inflammatory variables existed between the asthmatic children and a healthy control group, and whether these differences in inflammatory parameters are associated with lung function parameters. We observed that children, despite their treatment with ICS, do have ongoing eosinophilic activation at day and night and lymphocytic activation in daytime. Eosinophilic activation was related to the variability in airway diameter, whereas lymphocytic activation was associated with the level of FEV$_1$. Despite clinical improvement with salmeterol treatment, we could not find any improvement in inflammatory parameters in daytime, even though there was room for improvement given the observed differences in inflammatory parameters between healthy and asthmatic children treated with ICS.

**Final conclusions and recommendations**

Nocturnal symptoms are still frequently present in a population of children with asthma who are under control in an asthma outpatient clinic. FEV$_1$ seems to be a poor predictor for nocturnal symptoms, and doctors should specifically ask for these symptoms because this offers the opportunity to take adequate measures. Since the end of this epidemiological study on the frequency of nocturnal symptoms newer therapeutic options such as mattress encasings and drugs especially beneficial for nocturnal symptoms became available. It seems worthwhile to repeat such a study in the near future because this may give insight in possible shifts in nocturnal symptoms in this population.

The studies in this thesis add new insights to the concept on the pathophysiology of nocturnal airflow limitation in asthmatic children. Exogenous factors such as environmental tobacco smoke, the presence of pets, and high HDMA levels all independently contribute to the circadian PEF amplitude in allergic asthmatic
children. Parents should not only be stressed to stop smoking during pregnancy, but also any time thereafter to improve the stability and the prognosis of their child's asthma. Another important message is that pets contribute to an enhanced circadian PEF variability even in asthmatic children who do not express allergies to these pets. It seems appropriate to assess whether withdrawal of these pets improves asthma stability. HDM in mattresses provide the most important contribution to the circadian variation in airway diameter compared to other sources of HDM exposure.

Children with asthma are exposed to comparable HDM levels as healthy children. More smooth floor coverings were observed in asthmatic children probably as a result of earlier given advises. Smooth floors contained less HDM than carpeted floors, indicating that environmental advises should include the elimination of carpeted floors.

The concept of the circadian variation in airway diameter in asthmatic children that superimposed endogenous circadian rhythms such as for bronchial responsiveness, the autonomic central nervous system and cortisol secretion play an important and intricate role in the circadian modulation of the inflammatory process by changing numbers of cells, their release of mediators and/or the susceptibility of airway smooth muscle and vasculature needs further support. It is an attractive concept to hypothesize that endogenous secretion of cortisol conducts this inflammatory process. Low cortisol levels at night, or a more general lower cortisol secretion in asthmatic children with nocturnal symptoms oppose possible protection against inflammatory processes. This needs further investigation.

Long-acting β2-adrenergic bronchodilators are a good tool in the treatment of nocturnal airflow limitation. Even in stable asthmatic children who were already treated with ICS we observed a sustained bronchodilating effect of salmeterol and a reduction in circadian airflow limitation. We did not find a protective effect on bronchial responsiveness despite that all children had enough room to improve. We did not observe a rebound effect on bronchial responsiveness after cessation of salmeterol. Little evidence remains that salmeterol has anti-inflammatory properties.

Future studies on treatment of nocturnal symptoms in allergic asthmatic children should focus on optimal treatment regimes. Mattress encasings and long-acting β2-adrenergic drugs such as salmeterol seem to be successful interventions together with anti-inflammatory treatment with ICS. However, smoking cessation and pet avoidance should be advised in every child with unstable asthma.

References

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9. Summary, conclusions and recommendations


