Towards a rational dosing of corticosteroids in asthma
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INTRODUCTION
The studies described in this thesis were performed in patients with asthma. Asthma is characterised by episodes of dyspnea and/or wheezing and variable airway obstruction. Histopathologically, asthma is characterised by a chronic inflammation of the airways. The mainstream of asthma treatment consists of anti-inflammatory therapy and the use of inhaled corticosteroids is therefore advised in all asthma guidelines. This thesis aims at establishing the rationale for dosing strategies of inhaled corticosteroids in asthmatics using traditional and new techniques. The results of this thesis are summarised below.

ASThma GUIDELINES AND SELF-MAnAGEMENT PLANS
When physicians became more aware of the inflammatory pathophysiology of asthma, several asthma guidelines were developed. These guidelines included classification, medication plans, self-management plans, and management of exacerbations and were not uniform in their recommendations. In Chapter 2 a comparison of 5 international asthma guidelines was made. Guidelines differed for instance regarding the levels of severity of asthma at which ICS should be started. Additionally, the rules for stepping down the use of ICS received little attention, were imprecise, and had hardly been backed-up by adequate studies. One example of the latter is the GINA guideline that states: “if control is sustained for at least three months, a gradual stepwise reduction in treatment may be possible” "neither the definition of control nor the algorithm for dose reduction is provided. Treatment changes in self-management plans are generally guided by change in peak expiratory flow (PEF) and symptoms. We do not think that these parameters, especially PEF, are attractive for all patients in making a decision when and how to change the dosage of inhaled corticosteroids because monitoring by daily PEF measurements is not very practical in daily use (time consuming, stigmatisation, size of apparatus as carry-on luggage, Chapter 2). Additionally changes in ICS doses in self-management plans are dictated much more frequently by symptoms than by PEF changes (Chapter 11).

START THERAPY: ORAL OR INHALED CORTICOSTEROIDS
Most diagnosed patients with asthma have to start with anti-inflammatory therapy and patients who are not optimally treated have to augment this treatment. Several asthma guidelines state that fast suppression of inflammation and reduction in symptoms should be aimed for. It has been stated that a course of oral prednisolone (30-40 mg/day) is the best therapy in this situation. We investigated in Chapter 3 whether inhaled fluticasone could serve as an alternative treatment to oral corticosteroids in case of poorly controlled asthma. We expected a similar or slightly worse clinical response to fluticasone, but with a favourable side-effect profile. However, we found inhaled fluticasone in a dose of 2000 μg/day to be superior to oral prednisolone for two weeks (30 mg/day). This was specifically true when improvement of asthma control was assessed by tests of bronchial hyperresponsiveness (methacholine and adenosine-5’-monophosphate). A significant decrease of blood eosinophils and ECP was found with inhaled fluticasone 2000 μg/day compared to 500 μg/day. The clinical effects of a lower dose (500 μg/day) were comparable to oral prednisolone, but with less cortisol suppression. Serum cortisol, a
surrogate marker of systemic suppression by corticosteroids, appeared in our first analysis to be equally suppressed by oral prednisolone (30 mg/day) and fluticasone 2000 µg/day. This measurement of cortisol was performed by conventional RIA method and it was pointed out to us that cross-reaction with oral prednisolone occurs in analyses of cortisol by RIA. Re-analysis with an HPLC method showed that cortisol levels in serum were lower in the oral prednisolone group compared to the fluticasone 2000 µg/day group, which in turn was lower than in the fluticasone 500 µg/day group. Thus, systemic side effects, as measured with serum cortisol are less with high doses of inhaled fluticasone than with oral prednisolone, but are still clearly measurable.

PREDICTING CLINICAL BENEFIT FROM CORTICOSTEROIDS

In general, corticosteroids improve asthma symptoms yet this is not the case for all patients to the same extent. How well an individual patient with newly diagnosed asthma or with insufficient asthma control will respond to therapy is a common and clinically important question. In Chapter 4 we set out to determine whether we could predict a favourable short-term clinical response to corticosteroids in patients with asthma. We found that steroid induced changes in FEV₁, PC₂₀ Mch, and QOL were predominantly predicted by their respective baseline value and to a smaller extent by eosinophils in blood or sputum. The value of ECP levels measured in blood or sputum for predicting the response to corticosteroids was equal to, but certainly not better than eosinophil numbers. Unfortunately we found that the prediction of a good clinical response in an individual patient was poor. For instance, high sputum eosinophils (>3%) correctly predicted a significant improvement in PC₂₀ Mch in only 65% of the patients.

A NOVEL MARKER OF AIRWAY INFLAMMATION: EXHALED NITRIC OXIDE

Since 1993, the small molecule exhaled nitric oxide (eNO) can be measured in exhaled air. It was stated to be a non-invasive marker of airway inflammation in asthmatics. Early reports in international papers were enthusiastic about this new tool, stating that there was a clear-cut difference between asthmatics and healthy controls and that therefore one could easily discriminate between both groups. Moreover, the effects of ICS could be assessed by eNO. After the first reports, papers appeared reporting lesser discriminatory properties and pitfalls of measurements. Two different ways of measurement were used: the tidal breathing method and the single breath method. In Chapter 5 we compared both methods. We included asthma and COPD patients and compared them with healthy controls differentiating between non-smokers and ex- or current smokers. We found that mean eNO values were generally significantly higher with the single breath method than with the tidal breathing method in nonsmoking and in smoking asthmatics and especially so within the higher eNO ranges. This signifies that results are only comparable when the same method is being used. Exhaled NO levels were not significantly different between ex-smokers with COPD and healthy ex-smokers.

In further research we identified another pitfall of the eNO measurement. Exhaled NO is measured by the so called chemiluminescence method. The chemical reaction of NO with ozone was thought to be very specific. However, we found a sharp increase in eNO levels.
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after cleaning of the breathing system with an alcohol containing disinfectant. In Chapter 6 we investigated the difference in eNO readings after a small spill of alcohol into the breathing system versus a dry system free of alcohol containing disinfectants. We found a larger than 20% increase in exhaled NO readings in the presence of alcohol. This is an important factor in the accuracy of the measurement given the small differences found between asthmatics and healthy subjects. We advise during the day not to clean the breathing system with alcohol containing substances but only to change the mouthpiece to prevent changes in NO readings of exhaled air.

Chemiluminescence is influenced by more substances than ethanol alone. The influence of H₂O and CO₂ was studied in Chapter 7. A clear decrease of approximately 17% in NO readings was shown when the sample was saturated with water compared to dry gas. We therefore advise to insert a water absorber before exhaled air enters the chemiluminescence analyser.

When these pitfalls of measurement are well controlled for, we confirmed that eNO levels are very sensitive to corticosteroids and return to levels in the normal range both with a high and with a moderate dose of inhaled fluticasone (Chapter 3). Notwithstanding this, we found that eNO levels do not predict the response to steroids very well (Chapter 4).

AIRWAY INFLAMMATION IS MORE CLOSELY ASSOCIATED WITH PC₂₀ ADENOSINE-5’-MONOPHOSPHATE (AMP) THAN WITH PC₂₀ METHACHOLINE.

Measurement of bronchial hyperresponsiveness is traditionally performed with methacholine or histamine. These substances act as direct stimuli on airway smooth muscle receptors. AMP acts as an indirect stimulus with possibly a small direct effect on airway smooth muscle and a release of mediators by mast cells. In Chapter 3 we showed a larger corticosteroid induced improvement in PC₂₀ AMP compared to PC₂₀ methacholine. Therefore our hypothesis in Chapter 8 was that PC₂₀ AMP is more closely associated with inflammation than PC₂₀ methacholine. We analysed the cross-sectional association between airway hyperresponsiveness as measured by AMP or methacholine and airway inflammation. Inflammation was assessed by total cell counts and differentials as well as mediators (ECP and IL-8) in blood and sputum, as well as by exhaled NO (Chapter 8). Cross sectional analyses showed that the variation in PC₂₀ AMP was explained by percentage of sputum eosinophils and to a small extent by FEV₁ %predicted whereas variation in PC₂₀ Mch was mainly explained by FEV₁ %predicted and to a smaller extent by the percentage of blood monocytes. Moreover, the percentage of variance explained by the eosinophilic inflammation was larger for PC₂₀ AMP than for the PC₂₀ Mch.

In Chapter 9 we analysed the association between corticosteroid induced changes in inflammation and changes in PC₂₀ AMP or methacholine. Multivariate analyses showed that the improvement in PC₂₀ AMP responsiveness was solely related to the reduction in airway inflammation (i.e. change in the number of sputum eosinophils, lymphocytes, epithelial cells, and concentration of NO in exhaled air). In contrast, improvement in PC₂₀ methacholine was related to both the reduction in airway inflammation and the increase in FEV₁ %predicted. The total explained variance of the improvement in bronchial hyperresponsiveness was again greater for AMP than for methacholine (36% versus 22%, respectively). From these 2 studies we conclude that PC₂₀
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AMP is a more promising tool for monitoring airway inflammation and effects of anti-inflammatory therapy than PC_{20} methacholine. More prospective studies need, however, to be performed.

RISK OF OVERUSE OF INHALED CORTICOSTEROIDS IN SELF-MANAGEMENT PLANS

Asthma guidelines advocate the use of self-management plans. These guidelines advise to increase inhaled corticosteroids in a phase of unstable asthma but do not give clear guidance on how and when to reduce the dose of inhaled corticosteroids. We were afraid that this could lead to the use of relatively high doses of inhaled corticosteroids with unwanted systemic side effects. In Chapter 10 an asthma self-management plan was investigated in a one-year study that determined whether this self-management plan leads to the use of a relatively high dose of ICS. The study started with a relatively low dose of inhaled fluticasone (200 \( \mu \)g/day) and used PEF and symptoms as guidance for altering treatment. In our study we also included exact guidance for reduction of inhaled corticosteroids after a period of stable disease. A comparison was made with a group of patients with a fixed, conventional dose of inhaled fluticasone (500 \( \mu \)g/day). The study showed that there was no indication of 'overuse' of inhaled corticosteroids for most patients within the self-management group since a significantly lower mean dose of 275 \( \mu \)g/day was found in this group than the mean dose of 500 \( \mu \)g/day within the fixed dose group. No significant differences between both treatment strategies were found for both clinical and inflammatory parameters. Nevertheless, 3 patients were found who used > 2000 \( \mu \)g/day within the self-management group. These patients were characterised by a low asthma quality of life score at the start of the study (4.2 compared to 5.4 on a scale of 0-7). Since no other measured parameters differed with the remaining patients, these patients were labelled as "extreme perceivers" or "hyperperceivers". A search was also made which parameters could predict the end dose of inhaled fluticasone within the self-management group. Only serum IgE and asthma quality of life were found to be independent predictors for the end dose of steroids. Moreover, these predictors explained only 19% of the variance in end dose of steroids, which is relatively poor and of little value for choices in individual patients.

TYPES AND CHARACTERISTICS OF ASTHMA EXACERBATIONS

Corticosteroids are the mainstay of the treatment and prevention of asthma exacerbations. To study newly developed steroids and new intervention strategies, models of loss of asthma control and models of asthma exacerbations are sought for, and controlled steroid withdrawal has been used as such a model. Comparisons of steroid withdrawal and spontaneous (real life) exacerbations are presented in Chapter 11. We found striking differences between both types of exacerbations. Corticosteroid withdrawal exacerbations were characterised by a higher % of eosinophils in blood and sputum, IL-5 production by stimulated PBMC's, and exhaled NO levels compared to spontaneous exacerbations. The latter were characterised by a high % of neutrophils in sputum compared to steroid withdrawal exacerbations. This leads to the conclusion that steroid withdrawal...
exacerbations cannot be compared with spontaneous exacerbations during corticosteroid maintenance therapy, but reflect loss of asthma control in general.

ROLE OF VIRUSES AND DER P1 IN EXACERBATIONS
Triggers leading to an asthma exacerbation are still poorly understood. It is known that both upper respiratory tract viruses and inhaled allergens like house dust mite, a common allergen in Western Europe, can increase asthma symptoms and airway inflammation. We determined the presence of viruses in nasal aspirates during both an exacerbation and during a stable phase of the disease and found no significant differences between exacerbation and stable periods. We describe a novel technique to approach allergen exposure, i.e., measurement of allergen (Der p1) directly in sputum. Der p1 levels were detectable in 25% of the samples, and did not show clear elevations during exacerbations. The results do not support the importance of changes in Der p1 in relation to exacerbations of asthma in individuals.

CONCLUSIONS
The main conclusions derived from the studies and review in this thesis are:

- Asthma guidelines are not uniform in when and how to start with anti-inflammatory therapy. Additionally, they offer more explicit guidance in how to increase the dose of inhaled corticosteroids than in how to decrease them.

- Execution of self-management by patients is predominantly guided by changes in symptoms and less by changes in PEF measured by a PEF meter and therefore we prefer the use of symptoms above PEF, since the former can be more easily monitored by the patient.

- A high dose of inhaled fluticasone (2000 µg/day) given by Diskhaler is superior to oral prednisolone (30 mg/day) given as start therapy for treatment of instable asthma. This dose clearly reduces serum cortisol although less extensively so than prednisolone. The clinical effects of a lower dose (500 µg/day) are comparable to oral prednisolone, but with less cortisol suppression.

- Serum cortisol measurements by RIA method can be influenced by systemic prednisolone and should therefore be performed by HPLC method when prednisolone can be present.

- Prediction of benefits from corticosteroids in improving bronchial hyperresponsiveness, FEV1, and asthma quality of life is predominantly determined by their respective baseline values and to a smaller extent by blood and sputum eosinophils. The individual prediction of response is, however, poor. ECP levels do not have an additional value compared to blood or sputum eosinophils.
SUMMARY GENERAL DISCUSSION

- Exhaled NO measurements are influenced by many substances (H2O, ethanol, smoking). Levels of exhaled NO are most clearly elevated in corticosteroid naive patients. With proper measurements, exhaled nitric oxide is still not very useful as a marker of airway inflammation while monitoring asthma, since eNO is not elevated during spontaneous exacerbations under ICS treatment.

- Adenosine-5′-monophosphate is more closely associated with airway inflammation and more reflective of changes in inflammation with corticosteroid therapy than methacholine and should be tested prospectively in clinical trials as a marker to monitor eosinophilic inflammation in asthma.

- Asthma self-management generally does not lead to the use of high doses of inhaled corticosteroids. Patients using a self-management plan while having a low asthma quality of life score are at higher risk for ending up with relatively high doses of inhaled corticosteroids.

- Steroid withdrawal induced exacerbations of asthma have a more eosinophilic pattern while spontaneous exacerbations during maintenance treatment with inhaled corticosteroids have a more neutrophilic driven pattern. Exacerbations induced by steroid withdrawal seem to reflect poor asthma control in general, rather than to resemble spontaneous exacerbations.

- Viral particles measured by PCR in nasal secretions and Der p1 antigens measured by ELISA in induced sputum are detectable but are not elevated during ICS withdrawal and spontaneous asthma exacerbations compared to a stable phase of asthma.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Dosing of steroids
According to asthma guidelines it is agreed that all new patients with symptoms of asthma more than once a week should start with corticosteroids. Even in mild persistent asthma this reduces exacerbations. From our own and from other studies we know that steroid naive asthma patients do benefit from both oral and inhaled corticosteroids. Unexpectedly we found a superior efficacy of inhaled fluticasone propionate (1000 μg bid) versus oral prednisolone (30 mg/day) as measured by improvement of airway hyperresponsiveness and lung function while eosinophil levels were reduced comparably. In contrast to suggestions made in some asthma guidelines to start patients with newly diagnosed asthma on a course of oral steroids to gain quick and optimal control, we therefore suggest to start with inhaled corticosteroids instead of oral prednisolone. Whether this is also advisable for asthma exacerbations presenting at the emergency department is less clear, but has been given some credibility in recent trials. Full-scale trials of inhaled corticosteroids, or inhaled corticosteroids with long acting β2-agonists, for the treatment of exacerbations are justified. We submit that rare but serious side effects of oral steroids, such as the induction of diabetes, would be prevented when oral prednisolone could be averted. Furthermore, the institution of oral prednisolone is frequently delayed for some time early in the course of a