Inhaled corticosteroids in childhood asthma
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SUMMARY

Short-term studies in children have shown that inhaled corticosteroids are effective in the treatment of asthma. Although asthma is a chronic disorder of the airways, long-term studies are scarce. The results of the studies presented in this thesis have dealt with the effect of long-term treatment with the inhaled corticosteroid (budesonide) and the beta-2-agonist (salbutamol) on symptoms, additional use of bronchodilators, airway calibre, bronchodilator response, airway responsiveness and exercise-induced asthma.

In chapter 1, a general introduction on the definition, morphology and diagnosis of asthma is given. Several characteristics of asthma, such as airway obstruction, airway responsiveness, exercise-induced asthma and atopy are highlighted and discussed. Furthermore intervention of childhood asthma is summarised. The aims of the study are listed in the last paragraph of this chapter.

Chapter 2 describes selection of the patients and methods used in the main study (chapter 6).

Chapter 3 describes that weak relationships exist between clinical asthma severity, expressed as symptoms scores and additional bronchodilator use, and airway calibre, bronchodilator response, airway hyperresponsiveness (AHR), and diurnal peak expiratory flow (PEF) variation. From the literature it was concluded that inflammatory processes in the airways weakly correspond to symptoms of asthma, airway calibre, and airway hyperresponsiveness.

Chapter 4 presents the results of a study on the different ways to express the bronchodilator response (BDR) in children with asthma. In both children and adults with asthma bronchodilator response is often used to confirm the diagnosis of asthma, to indicate the degree of reversibility, to select subjects for intervention studies, and to evaluate treatment. However, there is no consensus in the literature how the BDR should be expressed, or what constitutes a significant response. We also investigated the relationship between the BDR and the nonspecific airway hyperresponsiveness to histamine. The change in FEV₁ (ΔFEV₁) 20 minutes after inhalation of 800 μg salbutamol was expressed in 4 ways: as an absolute difference (ΔFEV₁), as a percentage of predicted FEV₁ (ΔFEV₁%pred) or initial FEV₁ (ΔFEV₁%init), and as a percentage of the deficit in FEV₁ (ΔFEV₁%[pred-init]). ΔFEV₁%init and ΔFEV₁%pred were not related to age and stature of the children; ΔFEV₁%[pred-init] was related to stature, whilst ΔFEV₁ was related to both age and stature. All indices correlated with baseline FEV₁. However, this is an artefact introduced by relating change to baseline value rather than to the mean of baseline and final value. In fact BDR, expressed as ΔFEV₁%pred was only slightly greater in children with the lowest baseline airway calibre (p = 0.08), unlike ΔFEV₁%init: BDR was weakly related to AHR. We conclude that the BDR in children is best expressed as ΔFEV₁%pred, because this is not dependent on age, stature and baseline FEV₁. In addition BDR should not be taken as a measure of airway responsiveness to bronchoconstricting stimuli.
In chapter 5 the effects of 8 weeks treatment with inhaled corticosteroids and bronchodilators was compared with treatment with bronchodilator alone on airway caliber, airway responsiveness, the amplitude of diurnal variation in peak expiratory flow (PEF), and symptom scores in 27 children with mild asthma. After 4 and 8 weeks of treatment with budesonide and terbutaline $PC_{20}^{\text{FEV}}$ increased with 2.1 and 1.3 doubling doses respectively, compared to terbutaline alone. Mean morning PEF improved significantly in both groups. The change in afternoon and nocturnal PEF was significantly greater after budesonide plus terbutaline than after terbutaline alone. Mean $FEV_1$ and the amplitude of diurnal variation in PEF did not change significantly in either group. Peakflow reversibility only decreased in the budesonide group. There were no differences between treatments for cough and dyspnoea, but wheeze decreased significantly in the budesonide group. Thus, in children with mild asthma and increased airway responsiveness treatment with budesonide in addition to regular treatment with inhaled terbutaline over eight weeks leads to an improvement in airway responsiveness, an increase in afternoon and nocturnal PEF values, and a decrease in peak flow reversibility and symptoms of wheeze.

Chapter 6 describes the results of the first part of the long-term multicenter study. In a double blind study, 116 children with asthma were randomly assigned to treatment with an inhaled beta-2-agonist (salbutamol 0.2 mg; t.i.d.) plus an inhaled corticosteroid (budesonide 0.2 mg; t.i.d.) (BA+CS) or to an inhaled beta-2-agonist (salbutamol 0.2 mg; t.i.d.) plus a placebo (BA+PL). All children had moderate asthma with a forced expiratory volume in one second ($FEV_1$) of 55-90% of predicted and/or the ratio $FEV_1$/forced vital capacity ($FVC$) of 50-75%; the provocative dose of histamine which causes a 20% fall in $FEV_1$ ($PD_{20}^{\text{histamine}}$) ≤150 microgram. Endpoints were symptoms (symptom scores, use of additional bronchodilators, temporary prednisolone courses and absence from school), airway caliber ($FEV_1$, PEF), bronchodilator response, and airway hyperresponsiveness expressed as $PD_{20}^{\text{histamine}}$ and as between day PEF variation. After a median follow-up time of 22 months, 26 patients on BA+PL (45%) had withdrawn from randomized treatment, mainly due to asthma symptoms, compared with 3 withdrawals in the patients on BA+CS. All endpoints improved in the BA+CS group and remained unchanged in the BA+PL group. The period after which endpoints had stabilized in the BA+CS group differed for the various endpoints. For both pre-and postbronchodilator $FEV_1$ and PEF this took 2 months, for PEF variation 8 months, for symptoms about 18 months, whereas $PD_{20}^{\text{histamine}}$ did not show a plateau at a median follow-up time of 22 months. No serious side effects have been reported in either treatment group. The conclusion of this part of the study was that the addition of inhaled corticosteroid to an inhaled beta-2-agonist improves both clinical and physiological endpoints and that inhaled corticosteroid has an important place in the long-term therapy of children with asthma.

Chapter 7 describes the results of the effect of long-term treatment with inhaled corticosteroid on exercise-induced asthma (EIA) in 55 children. We also compared the time course of stabilization of EIA to that of other indicators of airway responsiveness, such as peakflow variation (PEF) and $PD_{20}^{\text{histamine}}$ (see Chapter 6). The children were participants of the previous study. After a median follow-up of 22 months, that study design had to be changed, because of the high number of drop-outs on BA+PL. At that
time the treatment regimen of all children who had not withdrawn was changed into BA+CS. At the moment of change, and after 2 and 8 months on BA+CS a treadmill exercise test was performed. Eighty two percent of the children who were treated with BA+PL from the beginning had EIA compared to 55% in those who were treated with BA+CS (p<0.05). After 2 and 8 months of treatment with BA+CS in the patients previously on BA+PL this percentage decreased to 59% and 55%, respectively, and was not significantly different between both groups. In the patients previously on BA+PL the mean fall in PEF after exercise decreased from 33% to 16% after 2 months and to 18% after 8 months. It was unchanged in patients on BA+CS from the beginning, being respectively 16%, 15%, and 15%. The time course of stabilization of EIA (2 months) was shorter than that of PEF variation (8 months) and \( P_{D_{20}} \) histamine (22 months). We conclude that long-term treatment with inhaled corticosteroid reduced the prevalence of EIA with about 33% and the severity with about 50%, and furthermore that the various stimuli of airway hyperresponsiveness act through different bronchoconstricting mechanisms.

Chapter 8 presents the second part of the long-term study which includes an extended follow-up for 28-36 months of the children on inhaled corticosteroid plus beta-2-agonist. In this chapter the further development of endpoints and the remission rate are described. A symptomatic remission was defined as being symptomfree during any 8 months period. Symptoms tended to improve during the whole follow-up period, the other endpoints except \( P_{D_{20}} \) histamine remained stable. \( P_{D_{20}} \) showed a plateau after 20 months, although at a subnormal level. Thirty-five patients (60%) achieved a period of remission at some time during the 28-36 months of treatment. However, 23 (66%) of these children had a relapse. It was concluded that long-term treatment with inhaled corticosteroid improves both clinical signs, airway caliber and airway responsiveness but brings only a minority of the patients into a long-lasting remission.

Only few studies describe the effect of cessation of inhaled corticosteroid after long-term use. Chapter 9 describes the third part of the main study. In that study we report on the effect of gradual diminishment and stopping of long-term treatment with inhaled corticosteroid on symptoms, airway calibre and airway responsiveness in a representative subgroup of the patients who were on BA+CS for 28-36 months. Thirty one children who had completed 28-36 months of treatment with BA+CS on July 1 1991, were asked to participate. Twenty eight children were double-blind randomized in a 1:2 ratio either to continue budesonide (n=8) during a period of 6 months or to decrease the dose of budesonide (n=20) within 2 months, followed by placebo for 4 months. Treatment with salbutamol 600μg daily was continued in all patients. In the tapering off group 8 children were withdrawn, mainly due to symptoms of asthma and 5 patients experienced exacerbations for which prednisolone was needed, compared with none in the continuous treatment group. After tapering off symptoms of asthma and additional bronchodilator use increased, and both \( FEV_1\%predicted \) and \( P_{D_{20}} \) histamine decreased, when compared with continuation of treatment. From this study we conclude that long-term treatment with BA+CS suppresses underlying mechanisms of asthma, but does not cure the disease.
CONCLUSIONS

Nowadays it is generally accepted that asthma is a chronic inflammatory disease. Therefore, inhaled corticosteroid is gradually becoming a first line choice in the treatment of moderate to severe asthma. In this thesis a number of studies have compared the effect of long-term treatment with BA+CS on symptoms, airway caliber, bronchodilator response, airway responsiveness and exercise-induced asthma in children with asthma to treatment with BA alone. We have shown that all indicators of asthma can be modulated by treatment with inhaled corticosteroid. However, the maximal effect of inhaled corticosteroid on these various characteristics of asthma seems to be time dependent. Stabilization of exercise-induced asthma and diurnal PEF variation occurred within 2 months, airway calibre after 4 months, symptoms after 18 months, whereas PD_{20} histamine stabilized beyond 24 months of treatment with inhaled corticosteroid. Symptoms and PD_{20} seem to be the most sensitive indicators in the follow-up and evaluation of treatment of asthma. Only a minority of the children came into a symptomatic remission or a complete remission after long-term treatment with inhaled corticosteroid. This indicates that even after three years of treatment with inhaled corticosteroid the underlying mechanisms are still present. Furthermore we found that symptoms, additional bronchodilator use and airway responsiveness increased and airway caliber decreased after stopping long-term treatment with inhaled corticosteroids. Finally we conclude that inhaled corticosteroids are very effective in the treatment of asthma, but that they do not cure asthma.

DIRECTIONS FOR FUTURE RESEARCH

We have shown that long-term treatment with inhaled corticosteroid is very effective in children with asthma, although only a minority come into a remission, and furthermore that its therapeutic effect disappears after discontinuation. In our study we decided to give all patients inhaled beta-2-agonist daily. However, in the light of recent studies there is now discussion concerning whether it might be preferable to give them as needed. In adults regular therapy with inhaled beta-2-agonist has been associated with deterioration of asthma, and increased risk of death or near death, although a causal relation has not been established. Therefore new studies are required to compare the effect of treatment with inhaled corticosteroid alone versus inhaled corticosteroid and inhaled beta-2-agonist on demand. Nowadays interest has centered on new anti-inflammatory drugs, such as nedocromil and fluticasone, and long acting beta-2-agonists, such as salmeterol and formoterol. Their role in the long-term treatment of children with asthma remains to be established.