Effect of inhaled corticosteroids on bronchial responsiveness in patients with "corticosteroid naive" mild asthma: a meta-analysis

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Abstract

***Background*—Inhaled corticosteroids are the most efficacious anti-inflammatory drugs in asthma. International guidelines also advocate the early introduction of inhaled corticosteroids in corticosteroid naive patients. A study was undertaken to assess the effects of inhaled corticosteroids on bronchial hyperresponsiveness in patients with corticosteroid naive asthma by conventional meta-analysis.**

***Methods*—A Medline search of papers published between January 1966 and June 1998 was performed and 11 papers were selected in which the patients had no history of treatment with inhaled or oral corticosteroids. Bronchial responsiveness to bronchoconstricting agents was considered as the main outcome parameter. Doubling doses (DD) of histamine or methacholine were calculated.**

***Results*—The total effect size of inhaled corticosteroids (average daily dose 1000 µg) versus placebo in the 11 studies was +1.16 DD (95% confidence interval (CI) +0.76 to +1.57). When only the eight short term studies (2–8 weeks) were analysed the effect size of the bronchoconstricting agent was +0.91 DD (95% CI +0.65 to +1.16). No relationship was found between the dose of inhaled corticosteroid used and the effect on bronchial responsiveness.**

***Conclusion*—This meta-analysis in patients with corticosteroid naive asthma indicates that, on average, high doses of inhaled corticosteroids decrease bronchial hyperresponsiveness in 2–8 weeks. It remains unclear whether there is a dose-response relationship between inhaled corticosteroids and effect on bronchial hyperresponsiveness.**

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Keywords: inhaled corticosteroids; corticosteroid naive asthma; bronchial hyperresponsiveness

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Asthma is a chronic inflammatory disease of the airways.[1] Inflammatory cells (mast cells, eosinophils, lymphocytes, and macrophages) are present even in patients with mild asthma.[2] Levels of bronchoconstrictor mediators such as histamine and prostaglandins, which are known to be associated with inflammation, are also increased in mild asthma.[3] Inhaled corticosteroids are the most effective anti-inflammatory drugs.[1] There are indications that early introduction of inhaled corticosteroids may prevent remodelling of the airway epithelium in patients with asthma and thus irreversible loss of lung function.[1] Recently revised international consensus reports on asthma therefore advocate the administration of inhaled corticosteroids not only in moderate and severe asthma, but also in mild asthma.[1 4] One of the new recommendations for rapid control of mild asthma is to start treatment with higher daily doses of inhaled corticosteroids (up to 1000 µg) than in earlier reports (200–400 µg).[5 6] Surprisingly, no systematic reviews on the effects of inhaled corticosteroids in patients with mild corticosteroid naive asthma are available to support this recommendation. Hatoum *et al* performed a meta-analysis of the effects of treatment with inhaled corticosteroids in patients with mild chronic asthma based on five published articles[7] and found a significant increase in the peak expiratory flow (PEF) after treatment. However, PEF was the only main outcome parameter used. No measure indicative of bronchial inflammation was included. Furthermore, the previous use of inhaled corticosteroids was not an exclusion criterion of the meta-analysis. It is therefore possible that in all cases the asthma was "mild" because of a previous successful treatment with inhaled corticosteroids.

We have therefore performed a meta-analysis of all randomised controlled studies of inhaled corticosteroids in patients with corticosteroid naive mild asthma. Patients with mild asthma have nearly normal spirometric values and few symptoms, while significant bronchial inflammation is present. Bronchial hyperresponsiveness (BHR), which is considered by many as an indirect measure of inflammation, was therefore used as the main clinical outcome parameter of the meta-analysis. We also assessed the minimum dose of inhaled corticosteroid and the minimum duration of treatment required to obtain a significant improvement in BHR.

Methods

INCLUSION AND EXCLUSION CRITERIA

Studies were only included if they reported trials on the clinical effects of inhaled corticosteroids in patients with corticosteroid naive mild asthma as indicated in the title or abstract, if they followed a randomised controlled design, and if they had a duration of at least two weeks. Exclusion criteria included a history of treatment with inhaled corticosteroids, absence of the assessment of BHR or the absence of

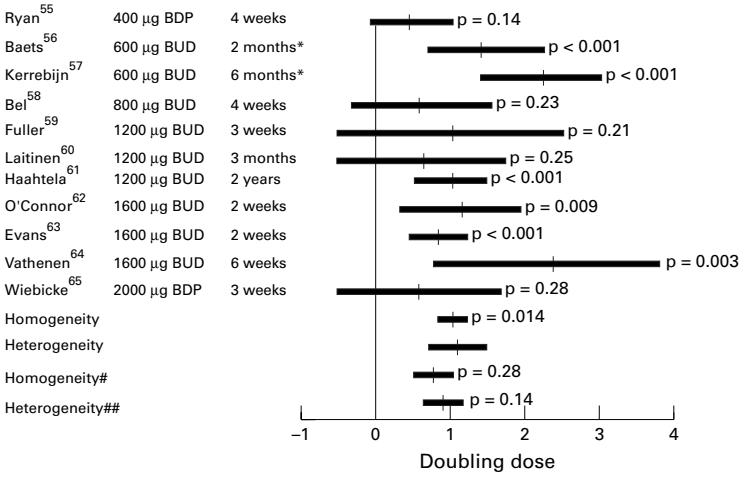

*Figure 1 Effect size of inhaled corticosteroids on bronchial responsiveness in doubling doses of bronchoconstricting agent with 95% confidence intervals and p values. The effect size within each selected study and the overall estimate are presented. Daily doses of inhaled corticosteroids are given. BUD = budesonide; BDP = beclomethasone; *studies in children; #only studies in adults; ## only studies of ⩽2 months.*

adequate data about the BHR (either original data or effect size with standard errors in both the inhaled corticosteroid and placebo groups).

SELECTION PROCEDURE

A Medline search was performed for papers published between January 1966 and June 1998 with the following "free text" words: "*beclomethasone*", "*budesonide*", "*fluticasone*", "*triamcinolone*", "*flunisolide*", "*inhaled (cortico)steroid(s)*", "*asthma(tic)(s)*", "*mild*", "*moderate*", "*(cortico)steroid naive*", "*newly detected*", "*newly diagnosed*", "*non(cortico)steroid dependent*". The search yielded 258 English references. All abstracts of the retrieved references were checked manually. Thirty nine papers concerned the pathophysiology of inhaled corticosteroids, 24 were general reviews or consensus reports on inhaled corticosteroids, and 20 discussed the adverse effects of inhaled corticosteroids. One hundred and three papers presented the effects of inhaled corticosteroids in various conditions such as rhinitis and pregnancy, and tolerance to β agonists. Seventy two papers included controlled as well as uncontrolled clinical trials of the clinical effects of inhaled corticosteroids in mild asthma. The reference lists of these studies were also checked for additional references.

By this method, 58 randomised controlled clinical trials assessing the effects of inhaled corticosteroids in patients with "mild to moderate asthma" were selected,[8–65] all but one of which[8] had a duration of two or more weeks. The method section of 39 of the remaining 57 papers stated that some of the patients included had a history of treatment with inhaled or oral corticosteroids.[9–47] These studies were excluded from the systematic analysis. In three studies[48–50] BHR had not been measured and these were excluded. Four of the 15 selected studies[51–54] contained data on the bronchoconstricting agent which were incomplete for estimating the true effect size (and SE) of inhaled corticosteroids versus placebo and therefore were not included in the analysis. Eleven studies were therefore left for inclusion in the meta-analysis. None of these studies assessed dose-response relationships.

QUALITY ASSESSMENT OF THE CONTROLLED STUDIES SELECTED

All 11 clinical trials selected for the review were checked by means of a criteria list for quality assessment of randomised clinical trials based on a recent Delphi consensus.[66] When the method section contained information about a specific item on the Delphi list a score of one point was given. In the absence of information or if there was a negative answer to a specific question zero points were given. The total score ranged from 0 to 9, a higher score representing a higher quality. Arbitrarily, studies with a score below 6 were judged to be of insufficient quality and were not reviewed.[66]

EVALUATION OF BRONCHIAL HYPERRESPONSIVENESS (BHR)

Bronchial hyperresponsiveness to bronchoconstricting agents was considered as the main outcome measure. The assessment of BHR differed widely between the studies, depending on the method (methods according to Hargreave,[52 55] Eiser,[56 57] Chai,[65] Sterk,[58] Yan,[64] or test method not mentioned[51 59–62]), the bronchoconstricting agent (histamine, methacholine, propranolol), and the expression method used (PD_{20}, PC_{15}, or PD_{35} in mg/ml, µg or µmol). Each of the agents was administered from the lowest concentration up to the minimal concentration inducing a specific fall in forced expiratory volume in one second (FEV_1). To compare the effects of inhaled corticosteroids on BHR between the studies, doubling doses (DD) of the triggers (log_2 transformed) were calculated (if not already done in the study). An increase of 1 DD of the trigger after treatment with inhaled corticosteroids meant that double the amount of the trigger was needed to achieve the same fall in FEV_1. In studies in which more than one irritant was used for the assessment of BHR only the most common irritant (histamine, methacholine) was evaluated.[56 59 62 65]

PROCEDURE OF THE META-ANALYSIS

In each study within the trial groups the difference in dose steps was determined by final minus baseline assessment. When values were expressed as log_{10} we used the formula log_{10}(final assessment) minus log_{10}(baseline assessment) divided by $log_{10}2$. To determine the SD of the differences, variances in the independent observations were used. When the variables x and y were considered, the variance was: $var(x—y) = var(x) + var(y)— 2 \times$ covariance (xy) or, in another formula: $var(x—y) = var(x) + var(y)—2 \times$ correlation coefficient $\times SD(x) \times SD(y)$. This correlation coefficient could only be assessed within the studies in which all individual data were presented. The mean of these coefficients was used as an "estimated" correlation coefficient within the remaining studies. The SD was assessed as the root of $var(x—y)$.

Table 1 Randomised controlled clinical trials on the effects of inhaled corticosteroids in patients with corticosteroid naive asthma

Study	*No. of patients, age, diagnosis*	*Duration of asthma*	*Main eligibility criteria*	*Design and duration*	*Intervention, daily dose*
Ryan[55]	10, 22–38 y, controlled, non-steroid dependent asthma	Not specified	Variability in FEV_1 >20%, BHR, only bronchodilators	DB, CO, 4 weeks	400 µg BDP vs. placebo, MDI
Baets[56]	31, 7–14 y, mild atopic asthma	Not specified	FEV_1 ⩾75%pred, cromoglycate and/or bronchodilators, no dependence on (oral) corticosteroids	DB, P, 2 months	600 µg BUD vs. placebo, MDI + spacer
Kerrebijn[57]	19, 7–16 y, allergic asthma	Not specified	PD_{20} methacholine <150 µg, FEV_1 ⩾80%pred, no continuous medication	DB, P, 6 months	600 µg BUD vs. 1500 µg terbutaline, MDI
Bel[58]	16, 19–38 y, mild atopic asthma	Not specified	Non-smoking, FEV_1 >80%pred, PC_{20} methacholine 1–7 mg/ml. No inhaled or oral corticosteroids in the past	DB, P, 4 weeks	800 µg BUD vs. placebo, Turbohaler
Fuller[59]	10, 18–45 y, atopic mild asthma	Not specified	Requiring only irregular therapy with inhaled β_2 agonists	DB, CO, 3 weeks	1200 µg BUD vs. placebo, MDI + spacer
Laitinen[60]	14, 21–59 y, newly diagnosed asthma	7.4 months (range 2–12)	No previous regular treatment	DB, P, 3 months	1200 µg BUD vs. 750 µg terbutaline, MDI + spacer
Haahtela[61]	103, 15–64 y, newly detected asthma	Symptoms <12 months	Symptoms <1 year, never used regular medication, FEV_1 reversibility >15%, PC_{15} histamine <32 mg/ml, no history of regular treatment or treatment with corticosteroids or cromoglycate	DB, P, 2 years	1200 µg BUD vs. 750 µg terbutaline, MDI + spacer
O'Connor[62]	12, 20–27 y, mild asthma	Not specified	BHR, atopy, only occasional symptoms controlled by β_2 agonist, FEV_1 >80%pred	DB, CO, 2 weeks	1600 µg BUD vs. placebo, Turbohaler
Evans[63]	10, 20–46 y, mild stable ashma	Not specified	FEV_1 >80%pred, atopic non-smoking, occasional symptoms controlled only by β_2 agonist	DB, CO, 2 weeks	1600 µg BUD vs. placebo, Turbohaler
Vathenen[64]	40, 18–45 y, mild to moderate asthma	⩾2 years	FEV_1 >50%pred, PD_{20} histamine ⩽4 µmol, current non-smokers, no treatment other than an inhaled β_2 agonist	DB, P, 6 weeks	1600 µg BUD vs. placebo, MDI + spacer
Wiebicke[65]	25, adults, asymptomatic or mild asthma	Not specified	FEV_1 >75%pred, no regular medication required, non-smokers, BHR present	DB, P, 3 weeks	2000 µg BDP + 800 µg salbutamol vs. placebo + 800 µg salbutamol, MDI + spacer

DB = double blind; P = parallel; CO = crossover; BDP = beclomethasone dipropionate; BUD = budesonide; MDI = metered dose inhaler; BHR = bronchial hyperresponsiveness; FEV_1 = forced expiratory volume in one second; PC_{20} or PD_{20} = concentration or dose of provocative agent required to reduce FEV_1 by 20% or more; DD = doubling dose.

Assessment of the overall effect size was based on the method of DerSimonian and Laird.[67] The effect size of inhaled corticosteroids versus control was assessed by subtracting the independent effects (effect of inhaled corticosteroid compared with placebo, unpaired *t* test). In fig 1 the effect size within each study is presented in DD with 95% confidence intervals (CI) and p values. The estimate was assessed under the condition of homogeneity. In case of significance (χ^2 test, $p<0.05$) the estimate was assessed under the condition of heterogeneity. Reasons for heterogeneity were investigated, if appropriate.

The doses of inhaled corticosteroids used were related to the effect sizes in two different ways. Firstly, a univariate regression analysis was used to relate increasing doses of inhaled corticosteroid to the effect size of BHR and, secondly, a Wilcoxon rank test was used to compare the effect size of high doses (⩾1000 µg daily) and low doses (<1000 µg daily) of inhaled corticosteroids. It is doubtful whether a dose of 600 µg daily is "low" for children, so we also assessed the dose-response relationship omitting the two studies in children.

To determine whether inhaled corticosteroids would be able to decrease bronchial responsiveness in short term studies we repeated the above analysis using only studies with a maximum duration of 2–8 weeks.

Results

QUALITY OF STUDIES

All 11 studies selected were of sufficient quality to be reviewed. Four studies were rated as being of high quality (score of 8)[57 58 61 64] and the remaining seven were of sufficient quality. Most of the 11 studies failed to give an explicit description of the method of concealed treatment allocation or intention to treat analysis.

METHOD OF STUDIES

Table 1 shows the study populations, eligibility criteria, design and intervention of the 11 studies. Two studies were performed in children with atopic asthma.[56 57] One study recruited 103 patients and was a long term study.[61] Patient numbers in the other studies varied from 10 to 40 subjects. Eligibility criteria differed widely between the studies, although all studies excluded subjects who had previously received regular treatment with inhaled corticosteroid. The duration of most of the studies varied from two weeks to three months. One study lasted six months,[57] and another for two years.[61] Nine studies compared the effects of inhaled corticosteroids with placebo and six with β_2 agonists. The average

Table 2 Randomised controlled clinical trials on the effects of inhaled corticosteroids in patients with corticosteroid naive asthma

Study	*Major outcome measures*	*Mean baseline BHR (range of doses applied)*	*Mean baseline FEV_1*	*Effects on BHR (inhaled corticosteroid vs. control)* *	*Effects on lung function (inhaled corticosteroid vs. control)*	*Effects on symptoms, β_2 agonists and bronchial epithelium/eosinophils (inhaled corticosteroids vs. control)*
Ryan[55]	PC_{20} histamine	0.5 mg/ml histamine (0.0125–16)	3.18 l	+0.44 DD (p = 0.14)	FEV_1 =	No data
Baets[56]	PD_{20} histamine/HDM	50 µg histamine (10–1280)	90%pred	+1.55 DD (p<0.001)	FEV_1+ (97%), morning PEF+ (20 l/min)	Symptoms =, β_2 agonists −
Kerrebijn[57]	PD_{20} methacholine	38 µg methacholine (10–1280)	95%pred	+2.33 DD (p<0.001)	FEV_1 =	Symptoms =
Bel[58]	PC_{20} methacholine, max airway narrowing methacholine	3.6 mg/ml methacholine (0.25–256)	94%pred	+0.65 DD (p = 0.23)	FEV_1 =	No data
Fuller[59]	PD_{35} histamine/bradykinin	0.28 µmol histamine (0.06–16)	89%pred	+1.00 DD (p = 0.21)	FEV_1 =, PEF+ (35–50 l/min)	Symptoms =
Laitinen[60]	PC_{15} histamine, FEV_1, PEF, symptoms, biopsy: bronchial epithelium, inflammatory cells mucosa	2.9 mg/ml histamine (1.0–32)	89%pred	+0.70 DD (p = 0.25)	FEV_1 =, PEF+ (50 l/min)	Symptoms =, β_2 agonists =, structure airway epithelium +, lymphocytes −, eosinophils −
Haahtela[61]	PC_{15} histamine, FEV_1, PEF, symptoms, β agonists	7.0 mg/ml histamine (1.0–32)	86%pred	+1.10 DD (p<0.001)	FEV_1 =, PEF+ (30 l/min)	Symptoms −, β_2 agonists −
O'Connor[62]	PC_{20} methacholine/MBS/AMP	1.4 mg/ml methacholine (0.125–32)	96%pred	+1.17 DD (p = 0.009)	FEV_1 =	No data
Evans[63]	Peripheral blood eosinophils, PC_{20} methacholine	0.13–2.23 mg/ml methacholine (0.125–32)	96%pred	+0.88 DD (p<0.001)	No data	No data about symptoms/β_2 agonists, eosinophils −
Vathenen[64]	PD_{20} histamine, FEV_1, PEF, symptoms, β agonists	0.37 µmol histamine (0.03–32)	95%pred	+2.40 DD (p = 0.003)	FEV_1+ (98%), PEF+ (40 l/min)	Symptoms −, β_2 agonists −
Wiebicke[65]	PC_{100} sRaw histamine/methacholine, PV_{75} sRaw hypervent/So_2	0.2 mg/ml histamine (0.01–8.0)	90%pred	+0.64 DD (histamine or methacholine) (p = 0.28)	No data	No data

BHR = bronchial hyperresponsiveness; DD = doubling dose; FEV_1 = forced expiratory volume in one second; PEF = peak expiratory flow; sRaw = specific airways resistance; So_2 = oxygen saturation; PC_{20}, PD_{20} = concentration or dose of provocative agent required to produce a fall in FEV_1 of 20% or more.; HDM = house dust mite. According to effects of inhaled corticosteroids versus control group on lung function and symptoms, '+' or '−' means statistically significant increase or decrease (p<0.05), '=' means no statistically significant difference. * See fig 1.

daily dosage of inhaled corticosteroids (budesonide or beclomethasone) used was 1000 µg (range 400–2000 µg).

EFFECTS ON BHR

Baseline BHR levels were in the mild asthmatic range in five of the studies[58 60–63] and in the moderate asthmatic range in the remaining studies (table 2).

The overall effect on BHR of inhaled corticosteroids compared with control was measured by accumulating the separate effect sizes of the 11 selected studies. For that purpose the original individual data[55 59 65] or mean $\log_{10}$ values, doubling doses, or geometric mean with SE or 95% CI of histamine or methacholine were subtracted[56–58 62–64] or assessed on the basis of the graphics[60 61] for all studies separately.

Effect sizes were all in favour of the inhaled corticosteroids, ranging from +0.44 to +2.40 DD of the bronchoconstricting agent (table 2). However, fig 1 shows that in five of the 11 studies the inhaled corticosteroid did not have a significant effect on BHR compared with placebo.[55 58–60 65]

The total effect size of inhaled corticosteroids versus placebo of the 11 studies was +1.16 DD (95% CI +0.76 to +1.57, test of heterogeneity) which was statistically significant. The confidence intervals of the effect size in the study by Baets *et al* in children did not fall within the confidence interval of the total effect size when assessed under conditions of homogeneity (p = 0.014). To determine whether heterogeneity could be explained by the variation in age we also assessed the total effect size without the two studies in children[56 57] but the total effect size remained statistically significant (+0.88 DD of the bronchoconstricting agent (95% CI +0.64 to +1.14)).

A univariate regression analysis was used to measure any dose-response relationship between the dose of inhaled corticosteroid and the level of BHR. This analysis showed no statistically significant relationship (regression coefficient –0.007 DD/100 µg, p = 0.87). Correcting for study duration did not improve the relationship between the dose of inhaled corticosteroids and decrease in BHR, nor was there a statistically significant effect found when the patients were divided into two groups according to the dose of inhaled corticosteroid (<1000 µg daily, four studies, total effect +1.25 DD; ⩾1000 µg, seven studies, total effect +1.13 DD; p = 0.92, Wilcoxon rank test). This difference in effect was somewhat higher than in the previous analyses (p values "fell" to p = 0.29 and p = 0.11, respectively) when the two studies in children (600 µg daily) were excluded.

We were also interested to determine whether inhaled corticosteroids were able to decrease BHR during short term treatment. A positive result was seen in four of the eight studies with a relatively short duration of 2–8 weeks[56 62–64] and a negative result was seen in the other four.[55 58 59 65] We combined the separate study effects in these short term studies to assess the overall effect size of inhaled corticosteroids compared with control on BHR. The effect size under the condition of homogeneity was +0.91 DD (95% CI +0.65 to +1.16) of the bronchoconstrictor in favour of the inhaled corticosteroid (p = 0.14). We also

related the effect sizes of individual studies to the dose of inhaled corticosteroids used in the short term studies by univariate regression analysis which gave a regression coefficient of +0.02 DD/100 μg (p = 0.38). Correcting for study duration did not improve the relationship between the dose of inhaled corticosteroids and decrease in BHR. A comparison of low dose (<1000 μg, 3 of 8 studies) versus high dose inhaled corticosteroids also showed a lack of correlation between the dose used and the level of BHR (+0.88 DD versus +1.21 DD, respectively; p = 0.55, Wilcoxon rank test).

Discussion

Inhaled corticosteroids are increasingly considered as first line treatment for asthma, even in milder stages of the disease.[1 4] The degree of BHR is considered to be indirectly related to the degree of bronchial inflammation. This meta-analysis in patients with corticosteroid naive asthma indicated that, on average, high doses of inhaled corticosteroids (mean dose 1000 μg, range 400–2000 μg daily) decreased BHR significantly within 2–8 weeks. This finding supports recent consensus reports recommending the use of relatively high initial doses of inhaled corticosteroids in mild bronchial inflammation.[1 4] There were insufficient studies to determine whether doses below 1000 μg daily would have been able to produce the same result.

Inhaled corticosteroids have been shown to be the most effective inhaled anti-inflammatory agents available for the treatment of asthma and there are indications that the early introduction of inhaled corticosteroids may prevent loss of lung function.[68] In patients with mild (corticosteroid naive) asthma the advantages of inhaled corticosteroids have to be weighed against the disadvantages. Local side effects such as oral candidiasis and systemic side effects such as adrenal suppression have been reported, especially with higher doses of inhaled corticosteroids.[69] It is important to recognise that control of BHR is an outcome which patients with few bronchial symptoms may not consider important and this may hamper patient compliance.

A few comments on the method of the meta-analysis have to be made. The purpose of the study was to assess the first time treatment effect of inhaled corticosteroids on bronchial inflammation so we searched the literature for studies of "corticosteroid naive" asthma. This may have led to confusion about the severity and duration of asthma of the studies included. Firstly, corticosteroid naive asthma is not necessarily mild, and patients with moderate to severe asthma could have been corticosteroid naive. Baseline BHR and FEV_1 in most of the studies suggested mild to moderate asthma. Unfortunately, the duration of asthma was not stated in many of the studies so asthma of recent onset as well as longer standing asthma (mild or moderate) might have been present.

The method of assessment of BHR varied widely between the studies. In order to compare different measurements of BHR the effects were presented in doubling doses of the trigger. Although the DD is often used as a clinical and epidemiological effect parameter, the comparison between the different studies may have resulted in some bias. However, both histamine and methacholine are the best validated substances for provocation testing.[70]

Type 2 errors could have occurred as a number of the studies analysed might not have had enough power. A conventional meta-analysis was therefore performed to obtain a tighter estimate of the effect size than that obtained by several smaller (and possibly underpowered) studies. However, we are aware that such an analysis may not totally overcome these shortcomings of individual studies.

We performed a meta-analysis despite the diversity of the studies included. The studies contained populations of different ages (children and adults), asthma of different duration (less than one year to unspecified) and of slightly different severity, the use of different inhaled corticosteroids, different dosages of inhaled corticosteroids, and different study durations (two weeks to two years). These differences might have influenced the reliability of the results to some extent. However, the direction of effect sizes was always the same, and the different dosages and duration of the studies made it possible to estimate dosage and time effects of drug activity.

In this study the measurement of BHR as a hallmark of inflammation in asthma was the primary outcome parameter of the effects of inhaled corticosteroids in patients with corticosteroid naive mild asthma. The clinical relevance of an overall effect size of approximately 1 DD of the trigger after treatment with inhaled corticosteroids of patients with corticosteroid naive asthma is not yet clear. This difference is thought to be clinically relevant in patients with moderate and severe asthma.[71] In those with corticosteroid naive asthma the improvement in BHR may be of greater importance because, in most cases, there is less room for improvement than in moderate and severe asthma. There are indications that bronchial inflammation precedes bronchial obstruction and thus probably symptoms in asthma.[72] Patients with corticosteroid naive (mostly mild) asthma may have nearly normal spirometric parameters and few symptoms on testing. Improvements with treatment are therefore difficult to obtain. Measurement of BHR was therefore chosen as an indicator of bronchial lability. Nevertheless, in half of the 11 studies analysed there was a significant improvement in lung function (PEF and/or FEV_1) after treatment with inhaled corticosteroids.[56 59–61 64] Three of the six studies in which symptoms or the use of bronchodilators were evaluated reported a statistically significant decrease in one of these parameters after treatment with inhaled corticosteroids.[56 61 64]

Most studies showed a clinically significant decrease in BHR after treatment with high doses of inhaled corticosteroids compared with the control drug. However, only in the two year study by Haahtela *et al* in patients with corticosteroid naive mild asthma did long term

treatment with a high dose of inhaled corticosteroids eventually cause BHR to return to "non-asthmatic" levels.[61] Although the first six weeks of treatment with inhaled corticosteroids contributed most to the effect on BHR, the PC_{15} histamine increased gradually during the two year study. A gradual decrease in the level of BHR during 12–24 months of treatment with inhaled corticosteroids was also reported in two studies in patients with moderate asthma.[73 74] The six month study by Kerrebijn *et al* and the three month study by Laitinen *et al* also found that the first 6–8 weeks of treatment with inhaled corticosteroids contributed most to the decrease in BHR.[57 60] In the light of these results we suggest that the dose could probably be tapered after six weeks to a lower dose (200–400 μg), both to avoid adverse effects and gradually to diminish the inflammation in the long term.

No relationship between the dose of inhaled corticosteroids and the level of BHR was found. It is possible that the only low dose study included in the analysis[55] (400 μg daily) was too short to show an optimum improvement within the study period of four weeks, so we cannot fully exclude the possibility of a dose-response effect. Unfortunately, no studies were analysed in which dose-response relationships were tested. Larger and more long term studies are urgently needed in patients with corticosteroid naive asthma to assess the effects of first time treatment with inhaled corticosteroids at different dosages and periods of treatment on both BHR and lung function and symptoms.

In conclusion, this meta-analysis has indicated that, on average, high doses of inhaled corticosteroids (mean dose 1000 μg, range 400–2000 μg daily) decreases BHR within 2–8 weeks in patients with corticosteroid naive asthma. It remains unclear whether lower doses of inhaled corticosteroids can achieve the same results. In the meantime it may be wise to follow the recent treatment protocols of consensus reports on asthma advocating a top-down strategy with inhaled corticosteroids once control of symptoms has been achieved.

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