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

Authors' objectives
To assess the effects of inhaled corticosteroids on bronchial hyperresponsiveness (BHR) in patients with corticosteroid naive asthma by conventional meta-analysis.

Searching
MEDLINE (January 1966-June 1998) was searched, and the search terms were provided. The reference lists of the retrieved articles were also checked for additional references.

Study selection
Study designs of evaluations included in the review
Only randomised controlled studies with a duration of at least two weeks were included.

Specific interventions included in the review
Inhaled corticosteroids.

The average daily dose of inhaled corticosteroids (budesonide or beclomethasone dipropionate) used was 1000 micrograms (range 400 - 2000 micrograms).

Participants included in the review
Patients (adults and children) with corticosteroid naive mild asthma and no history of treatment with inhaled or oral corticosteroids.

Outcomes assessed in the review
Bronchial hyperresponsiveness (BHR) was the main clinical outcome. Studies were excluded if they did not report adequate data about the BHR (either original data or effect size with standard errors in both the inhaled corticosteroid and placebo groups). The minimum dose of inhaled corticosteroid and the minimum duration of treatment required to obtain a significant improvement in BHR was also assessed.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
Trials were assessed by means of a criteria list for quality assessment of randomised clinical trials based on a recent Delphi consensus (see Other Publications of Related Interest). 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. The authors do not state how the papers were assessed for quality, or how many of the authors performed the quality assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.
Methods of synthesis
How were the studies combined?
To compare the effects of inhaled corticosteroids on BHR between the studies, doubling doses (DD) of the triggers (log transformed) were calculated (if not already done so 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 FEV1.

In each study within the trial groups, the difference in dose steps was determined by final minus baseline assessment.

Assessment of the overall effect size was based on the method of DerSimonian and Laird (See Other Publications of Related Interest). 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). The effect size within each study was presented in DD with 95% confidence intervals (CI) and p values. The estimate was assessed under the condition of homogeneity. In case of significance (chi-squared test <0.05) the estimate was assessed under the condition of heterogeneity.

The doses of inhaled corticosteroids used were related to the effect sizes in two ways. Firstly, a univariate 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 (greater than or equal to 1000 millionths of a gram daily) and low doses (less than or equal to 1000 millionths of a gram daily) of inhaled corticosteroids. The dose response relationship was also assessed after omitting two studies involving children.

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

How were differences between studies investigated?
Chi-squared tests for heterogeneity were performed. Reasons for heterogeneity were investigated, if appropriate.

Results of the review
Eleven studies, comprising 290 participants were included.

Four studies were rated as being of high quality (score of 8) and the remaining 7 were of sufficient quality.

Baseline BHR levels were in the mild asthmatic range in five of the studies and in the moderate asthmatic range in the remaining studies. Effect sizes were all in favour of the inhaled corticosteroids, ranging from 0.44 to 2.40 DD of the bronchoconstricting agent. However, in five of the 11 studies, the inhaled corticosteroid did not have a significant effect on BHR compared with placebo.

The total effect size of inhaled corticosteroids versus placebo was 1.16 DD (95% CI: 0.76, 1.57, test of heterogeneity), which was statistically significant. To determine whether heterogeneity could be explained by the variation in age the total effect size was assessed without the two studies involving children. The total effect size remained statistically significant (0.88 DD of the bronchoconstricting agent; 95% CI: 0.64, 1.14).

A univariate regression analysis showed no statistically significant dose-response relationship between the dose of inhaled corticosteroid and the level of BHR (regression coefficient -0.007 DD/100 micrograms, p=0.87). Correcting for study duration did not improve the relationship between the dose of the 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 the inhaled corticosteroid (<1000 micrograms daily, four studies, total effect 1.25 DD; greater than or equal to 1000 micrograms, seven studies, total effect 1.13 DD; p =0.92, Wilcoxon rank test).

Inhaled corticosteroids were able to decrease BHR during short term treatment (2-8 weeks) in four of the eight studies, but a negative result was found in the other four. The separate study effects in these short term studies were combined 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, 1.16) of the bronchoconstrictor in favour of the inhaled corticosteroid (p=0.14).
In addition, the effect sizes of individual studies were related 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 micrograms (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 micrograms, 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.

**Authors’ conclusions**

This meta-analysis in patients with corticosteroid naive asthma indicates that, on average, high doses of inhaled corticosteroids decreases BHR within 2-8 weeks. It remains unclear whether lower doses of inhaled corticosteroids can achieve the same effect.

**CRD commentary**

The review addressed a well defined question, and reported appropriate inclusion and exclusion criteria. Sufficient details of the primary studies were provided, and the studies were combined appropriately.

The search could have been extended to include other databases, such as EMBASE, and an attempt to identify unpublished literature. Publication bias cannot be ruled out. Although the quality of the included studies was assessed, the items assessed by the Delphi quality assessment list were not stated.

The authors note that the method of assessment of BHR varied between studies.

The conclusions follow from the results.

**Implications of the review for practice and research**

Practice: The authors suggest that 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.

Research: The authors suggest that more research is required to explore the relationship between the dose of inhaled corticosteroids and the level of BHR found (dose response relationship). In addition, 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 symptoms.

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