Dose-response relationship of inhaled corticosteroids and cataracts: a systematic review and meta-analysis


CRD summary
The review found that among adults who used inhaled corticosteroids, risk of cataracts increased by about 25% for each 1,000µg increase in daily dose of beclomethasone dipropionate. Limitations that included a lack of randomised evidence, a small number of studies, possible duplication of data, statistical heterogeneity and failure to assess study quality, mean that the authors’ conclusions require cautious interpretation.

Authors’ objectives
To evaluate the dose-response relationship between inhaled corticosteroids and risk of cataract in adults.

Searching
MEDLINE and EMBASE were searched to January 2007. Search terms were reported. Reference lists of relevant studies were checked.

Study selection
Case-control studies of inhaled corticosteroid use and cataracts were eligible for inclusion provided they included at least two different doses of inhaled corticosteroids reported as the equivalent daily dose of beclomethasone dipropionate. Studies were required to report odds ratios (ORs) and confidence intervals (CIs) for the risk of cataracts for each dose of inhaled corticosteroids compared with non-use of inhaled corticosteroids and to adjust for potential confounders.

Data in the review derived from two health databases (one Canadian and one British) each used by two of the included studies. Most studies included only older adults (minimum age 40 or 65 years). Participants had chronic obstructive airways disease or asthma in the only study that reported this information. Studies included one to five matched controls for each case. All studies adjusted for use of systemic corticosteroids and a range of other variables such as gender, age, disease severity and consultation rate. Average daily inhaled corticosteroid dose was based on prescription history. Duration of exposure ranged from a single prescription to over five years. Ascertainment of cataract in the included studies was based on recorded diagnostic codes. There was no differentiation by type of cataract. The primary outcome of the review was risk of cataracts, expressed per 1,000µg increase in daily dose of inhaled beclomethasone dipropionate.

Two reviewers independently selected the studies.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Within each study an odds ratio (OR) and 95% CI were extracted for each dose of inhaled corticosteroids compared with non-use of inhaled corticosteroids, adjusted for confounders. The reviewers used published methods (Greenland 1992) to estimate the correlation of odds ratios reported within each trial and for each study calculated a slope coefficient (expressed as a log OR) and an odds ratio with 95% CI that related risk of cataracts to inhaled corticosteroid dose increase. The midpoint or mean of each dose range used within each study was used in the calculations, with a minimum dose of zero and maximum of 2,000µg.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Slope coefficients from individual studies were pooled by an inverse weighting variance method to calculate a pooled odds ratio and 95% CI. Results of both fixed-effect and random-effects models were reported. Results were presented as a graph with a zero intercept and a fitted risk. Heterogeneity was measured using $I^2$ tests. As one study reported two adjusted analyses (using different variables), a sensitivity analysis was performed that used each of these. It was planned to investigate heterogeneity by meta-regression, but there were too few studies. Publication bias was assessed by a funnel plot and formal test.

**Results of the review**

Four retrospective case-control studies were included (n=46,638 cases, 146,378 controls).

Inhaled corticosteroid dose was significantly related to risk of cataract. Each 1,000µg increase in daily dose of beclomethasone dipropionate or equivalent increased the risk of cataract by about 25% (OR 1.25, 95% CI 1.14 to 1.37; four studies, $I^2=66\%$, random effects)

There was no indication of publication bias.

**Authors’ conclusions**

Among adults who used inhaled corticosteroids, risk of cataracts increased by about 25% for each 1,000µg increase in daily dose of beclomethasone dipropionate or equivalent.

**CRD commentary**

The objective and inclusion criteria of the review were clear. Relevant sources were searched for studies. No specific efforts were made to retrieve unpublished studies, so it was possible that studies were missed. Although no evidence of publication bias was found on formal testing, this finding was unreliable with so few studies (as the authors noted). It was unclear whether language restrictions were planned, but in the event all studies found were in English. Two reviewers selected studies, which reduced risks of bias and error; the process used for data extraction was not described. It did not appear that study validity was assessed. These factors made it difficult to determine the reliability of the reported results. The four included studies derived their data from the same two databases and (as the authors noted) the study populations may have overlapped. This potential duplication of data reduced confidence in the review findings because it may have resulted in overly narrow confidence intervals. The studies may have used overlapping datasets, but their findings differed greatly, which suggested that the results may have been highly sensitive to the methods used. Statistical methods used to combine the studies were described in detail and appeared appropriate. Suitable methods were used to assess and explore heterogeneity. There was very marked statistical heterogeneity in the primary analyses and this was largely unexplained. The authors noted a number of sources of potential bias, which included lack of information about total exposure time and noncompliance with inhaled corticosteroid prescriptions. Manufacturers of drugs evaluated in this review had provided funding to the Medical Research Institute of New Zealand and to one of the reviewers for other work.

In view of limitations that included a lack of randomised evidence, a small number of studies, possible duplication of data, statistical heterogeneity and failure to assess study quality, the authors’ conclusions require cautious interpretation.

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

**Practice:** The authors stated that it was important to prescribe the lowest effective dose of inhaled corticosteroid therapy for asthma and chronic obstructive pulmonary disease (COPD) and that older individuals with these disorders (especially current or past smokers) should be screened for cataracts.

**Research:** The authors stated that there was an urgent need to determine how inhaled corticosteroid dose related to efficacy for treating COPD, so that the risk-benefit profile can be established.

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