Clinical safety of inhaled corticosteroids for asthma in children: an update of long-term trials

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CRD summary
This review aimed to assess the safety of long-term use of inhaled corticosteroids in children with asthma. The author concluded that daily doses of inhaled corticosteroids up to 400 micrograms can be used in children with asthma without clinically relevant systemic adverse effects. However, due to several limitations of the review, these conclusions should not be assumed to be reliable.

Authors' objectives
To assess the safety of long-term use of inhaled corticosteroids in children with asthma.

Searching
The MEDLINE and BIOSIS Previews databases were searched for relevant published studies up to July 2005. Search terms were reported. In addition, other review articles were checked for relevant studies.

Study selection
Prospective randomised controlled trials (RCTs) of at least 12 months duration were eligible for inclusion in the review. Studies selected for the review compared inhaled beclometasone, budesonide, fluticasone propionate (at a range of doses) against placebo or non-steroidal treatments in children. Across the included studies, children ranged in age from 0.4 to 17 years. Patient follow-up ranged from 12 months to 6 years.

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

Data extraction
The main characteristics of the included studies were extracted and presented in tables, including the outcomes of interest that were measured: statural growth, bone mineral density (BMD) or cortisol levels. The author did not state how data were extracted for the review.

Methods of synthesis
The results of the included studies were briefly presented in the text and tables of a narrative synthesis. The studies were grouped by the outcome measured: statural growth, BMD or cortisol levels.

Results of the review
Statural growth (14 studies, n=unclear):
Five RCTs compared low-dose inhaled corticosteroids (100-200 micrograms per day) with placebo or non-steroidal therapy. None of these found that inhaled corticosteroids exert any overall adverse effect on statural growth. Seven RCTs compared higher-dose inhaled corticosteroids (336-1,000 micrograms per day) with placebo or non-steroidal therapy. With the exception of one study that found 600 micrograms per day budesonide had no impact on growth over 22 months compared to placebo, all found some degree of apparent growth retardation in children treated with high-dose inhaled corticosteroids. Two RCTs compared fluticasone propionate (200 micrograms) against beclometasone (200 micrograms per day via dry-powder inhaler or 400 micrograms per day via pressurised metered dose inhaler), both of which reported a significantly higher growth rate in children receiving fluticasone propionate.

BMD (4 studies, n=unclear):
All four RCTs reported that inhaled corticosteroid therapy had no effect on BMD.

Cortisol levels (10 studies, n=unclear):

In general, studies of recommended doses of inhaled corticosteroids found little or no effect on measures of hypothalamic-pituitary-adrenal (HPA) axis function over 12 to 36 months follow-up. Two RCTs compared fluticasone propionate (200 micrograms) against different doses of beclometasone. One study found no difference between fluticasone propionate and beclometasone 200 micrograms per day. The second study found a significant reduction in mean serum cortisol levels versus baseline in children receiving 400 micrograms per day beclometasone from week 10 to month 20, with no reduction in the fluticasone propionate group.

Authors' conclusions
The available data indicate that daily doses of inhaled corticosteroids up to 400 micrograms can be used in children with asthma without clinically relevant systemic adverse effects.

CRD commentary
The review question was only explicitly defined in terms of study design, though the kinds of interventions and participants considered relevant were implied in the objective of the review. However, despite the stated restriction to prospective RCTs, the review also incorporates the results of several non-randomised studies, but it is not clear if these were identified in a systematic manner. The search for RCTs covered electronic databases and existing reviews, but was limited to published trials and it is unclear if there were language restrictions. Therefore, the potential for publication and language biases cannot be ruled out. No attempt was made to distinguish between the included RCTs in terms of methodological quality. The review appears to have been conducted by a single author, so there would appear to have been no independent validation of the selection and data extraction processes. The synthesis briefly summarises the included studies, but in many cases crucial details of individual studies (e.g. numbers of participants, mean outcome values) are not reported, with most studies simply described as having 'significant' or 'non-significant' effects on the outcomes of interest. As a consequence of these limitations, the conclusions of the review should not be assumed to be reliable.

Implications of the review for practice and research
Practice: The author did not state any implications for practice.
Research: The author stated that more research is needed in paediatric populations, particularly in younger children with long term follow-up over several years. In addition, the author stated that further studies are required on the long-term use of higher doses of corticosteroids in children before firm conclusions can be drawn.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.