Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis

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**Authors' objectives**
To appraise the systemic adverse effects of inhaled corticosteroids.

**Searching**
The authors searched the MEDLINE, EMBASE and BIDS electronic databases (January 1, 1966 to July 31, 1998) using 30 key search terms. In addition, the bibliographies of eligible articles and reviews were used along with scientific session abstracts in key respiratory and allergy based journals.

**Study selection**

**Study designs of evaluations included in the review**
The authors did not state an a priori research design. Included studies were randomised controlled trials (RCTs), prospective and retrospective cohort studies, cross-sectional studies, longitudinal studies, case-control studies and questionnaires. Some of the RCTs were open and/or crossover in design. Only 13 of the studies were double-blinded.

**Specific interventions included in the review**
The authors stated an a priori intention to look at inhaled corticosteroids. The studies included in the review looked at both inhaled and oral corticosteroids.

Interventions included inhaled corticosteroids (triamcinolone acetonide, fluticasone propionate, budesonide, beclomethasone dipropionate, or flunisolide), and salmeterol xinafoate, cromolyn sodium, theophylline, albuterol sulfate and budesonide as intervention or control or bronchodilator or placebo.

The oral corticosteroid prednisone was used in control groups. Interventions were administered orally or by using inhalers (pressurised metred-dose inhaler (pMDI), dry powder inhaler (DPI), or spacer). Doses ranged from 0.1 to 2.0 mg/day for inhaled corticosteroids and 2 to 20 mg/day for oral corticosteroids.

**Participants included in the review**
Healthy volunteers as well as asthmatic children and adults. For children, ages ranged from 1 to 15 years (mean age within studies ranged from 6.2 to 13 years). For adults, mean age within studies ranged from 28 to 60 years.

**Outcomes assessed in the review**
Adverse effects on adrenal gland, growth, bone, skin, and eye.

**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 reviewers performed the selection.

**Assessment of study quality**
No formal assessment of quality was undertaken. However, to be included, eligible studies had to provide sufficient information on patient demographics, study design, randomisation and control procedure, route of drug administration, measurement of end points, and data analysis.

**Data extraction**
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.
Data were extracted for the categories of study identification and year of publication, study design and number of participants (some listed ages of participants), intervention (dose, and mode of delivery), and outcomes. Data were extracted into three tables for the outcomes of adrenal suppression, medium- and long-term controlled growth, bone density.

Methods of synthesis
How were the studies combined?
Studies of adrenal suppression were combined in a multiple regression analysis for serum cortisol levels (13 studies) and urinary cortisol levels (21 studies). In these analyses model fitting was applied using multiple regression analyses of slopes to determine whether there were significant differences in slope gradients between treatments. The studies were weighted according to their sample size.

Differences between slope gradients were also calculated using 95% confidence intervals (CIs).

There were insufficient data to statistically combine the other end points so these were discussed in a narrative review of those studies.

How were differences between studies investigated?
Differences between studies were discussed in a narrative. The authors note that the review was mainly qualitative due to the variation in selected end points and a meta-analysis could not be performed.

Results of the review
The total number of studies is not stated in the review. The review includes 27 studies for adrenal gland suppression endpoints, 12 studies for the growth end point, 10 studies for the bone metabolism end point, and 2 studies for the skin effects endpoints. The number of studies for the ocular end point is not clear in the discussion.

Marked adrenal suppression occurs with high doses of inhaled corticosteroid above 1.5 mg/d (0.75 mg/d for fluticasone propionate) although there is a considerable degree of interindividual susceptibility. Meta-analysis showed significantly greater potency for dose-related adrenal suppression with fluticasone compared with beclomethasone dipropionate, budesonide, or triamcinolone acetonide, whereas prednisolone and fluticasone propionate were approximately equivalent on a 10:1 mg basis.

Inhaled corticosteroids in doses above 1.5 mg/d (0.75 mg/d for fluticasone propionate) may be associated with a significant reduction in bone density, although the risk for osteoporosis may be obviated by postmenopausal estrogen replacement therapy.

Although medium-term growth studies showed suppressive effects with 400 microg/d beclomethasone dipropionate, there was no evidence to support any significant effects on final audit height.

Long-term, high-dose inhaled corticosteroids exposure increases the risk for posterior subcapsular cataracts, and, to a much lesser degree, the risk for ocular hypertension and glaucoma. Skin bruising is most likely to occur with high-dose exposure, which correlates with the degree of adrenal suppression.

Authors’ conclusions
The authors state that all inhaled corticosteroids exhibit dose-related systemic adverse effects, although these are less than with a comparable dose of oral corticosteroids. Meta-analysis showed that fluticasone propionate exhibits greater dose-related bioactivity compared with other available inhaled corticosteroids, particularly at doses above 0.8 mg/d. The authors state that the long-term systemic burden will be minimised by always trying to achieve the lowest possible maintenance dose that is associated with optimal asthmatic control and quality of life.

CRD commentary
This systematic review is not well reported. Although the authors have stated the research question, the inclusion and
exclusion criteria were not stated a priori other than that studies should meet the requirement of sufficient data should be available in included studies for certain categories needed to perform the review. The literature search covered several databases and included searches for unpublished and grey literature. It is not clear whether there were any language restrictions.

The quality of the included studies was not formally assessed and the authors have not reported how the articles were selected, or who performed the data extraction.

The data extraction is reported in tables. It is not clear which studies (and participants) were included for each end point. Statistical pooling was performed for only one of the end points using meta-regression because of the variation in selected end points. There were no additional tests for heterogeneity although there was a narrative discussion of heterogeneity and biases. The remaining studies were combined in a narrative discussion.

The scope of the review is large, but very little detail of the process of the review is reported. For this reason, the authors' conclusions should be treated with caution.

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

Practice: The authors state that the long-term systemic burden will be minimised by always trying to achieve the lowest possible maintenance dose that is associated with optimal asthmatic control and quality of life.

Research: The authors do not state any implications for further research.

**Bibliographic details**

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Other publications of related interest
This additional published commentary may also be of interest. Honig PK. Review: high-dose inhaled corticosteroids increase the risk for some systemic adverse effects in asthma. Evid Based Med 1999;4:191.

**Indexing Status**

Subject indexing assigned by NLM

MeSH
Administration, Inhalation; Administration, Topical; Androstadienes /administration & dosage /adverse effects; Anti-Asthmatic Agents /administration & dosage /adverse effects; Anti-Inflammatory Agents /administration & dosage /adverse effects; Asthma /drug therapy; Beclomethasone /administration & dosage /adverse effects; Bone and Bones /drug effects /metabolism; Budesonide /administration & dosage /adverse effects; Dose-Response Relationship, Drug; Eye /drug effects; Fluticasone; Glucocorticoids; Growth /drug effects; Humans; Prednisolone /administration & dosage /adverse effects; Skin /drug effects; Triamcinolone /administration & dosage /adverse effects

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Record Status
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.