Dose response to inhaled corticosteroids: benefits and risks

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Authors' objectives
To systematically review the dose-response effects of inhaled corticosteroids in terms of their antiasthmatic efficacy and systemic adverse effects.

Searching
MEDLINE, EMBASE, and BIDS were searched from 1966 to 1997. Search terms are listed. Papers with subject headings or an abstract in English were included. Abstracts from scientific sessions from the American Journal of Respiratory and Critical Care Medicine, the Journal of Allergy and Clinical Immunology, Thorax and the European Respiratory Journal between 1993 and 1997 were also searched.

Study selection
Study designs of evaluations included in the review
All studies which contained an evaluation of at least two doses of a drug. Randomised (parallel group and crossover design), single blind, double blind or open. Some studies were placebo controlled.

Specific interventions included in the review
Triamcinolone acetonide (0.2 - 1.6 mg/day); Budesonide (0.1 - 3.2 mg/day); Fluticasone propionate (0.05 - 2.0 mg/day); Beclomethasone dipropionate (0.2 - 1.6 mg/day); Flusinolide (1.0 - 4.0 mg/day); Prednisone/ Prednisolone (7.5 - 40 mg/day); Betamethasone valerate (0.8 mg/day); Budesonide and Fluticasone propionate (0.1 - 0.4 mg/day). Drugs were administered by dry powder inhaler, metered dose inhaler, spacer or given orally. Duration of treatment ranged from 1 week to 1 year. Placebos have been given as control group treatments in some trials and other control treatments may have been given but are not reported in the review.

Participants included in the review
Adults and children with mild, moderate or severe asthma.

Outcomes assessed in the review
Forced expiratory volume in 1 second (FEV1), peak expiratory flow (PEF), adrenal suppression (HPA - axis suppression), growth effects, bone effects, effects on eyes, skin and leucocytes.

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
The authors do not state that validity was assessed.

Data extraction
The authors do not state how many reviewers extracted the data or how disagreements were resolved. Data were extracted on study design, number of participants, severity of asthma, treatments given, main findings. For adverse effects on adrenal suppression and growth, data were also extracted on measures used.

Methods of synthesis
How were the studies combined?
Meta-analysis was possible only for end points of adrenal suppression. All responses were calculated as percentage
adrenal suppression from placebo or baseline. The data were then analysed as percentage suppression versus log dose. Weighted model fitting was applied using multiple regression analysis to determine whether there was a significant difference between drugs for overall dose-response relationship. Where a significant difference was identified the 95% confidence interval was calculated.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
Efficacy analysis: 23 studies included (n=4280). 20 studies were of randomised design.

Adrenal suppression analysis: 13 studies included (n=245). All studies were of randomised design.

Growth effects analysis: 10 studies included, 4 short-term, 6 long-term (n=3815). All of the short-term studies and one of the long-term studies were of randomised design.

Biochemical bone markers analysis: 9 studies included (n=193). All studies were of randomised design.

Bone density analysis: 6 studies included (n=610). All included studies were of cross-sectional design.

It is unclear how many studies were included in the analysis of effects on eye, skin and leucocytes, or whether these were reviewed in a systematic way.

Efficacy: Two studies showed that doses ranging from 0.2 - 1.6 mg/day of either triamcinolone acetonide via spacer or budesonide via dry powder inhaler were all more effective than placebo; there was a plateau in response at more than 0.4 mg/day. Fluticasone propionate was effective in improving morning PEF, though the dose response curve was fairly flat between 0.1-0.8 mg/day, making it unclear which dose would be most effective. Budesonide and fluticasone were found to be equally effective in children (1 study) when given in dry powder inhalers. One study found no difference in clinical response between 1 mg/day and 2 mg/day fluticasone given via metered dose inhaler. In people with prednisone dependent severe asthma high doses of inhaled fluticasone appeared to have a more favourable effect than maintenance prednisone therapy.

Adrenal suppression: results of the meta-analysis were as follows, fluticasone (p<0.001), budesonide (p<0.001), beclomethasone (p<0.005), triamcinolone (p=0.25). The slope gradient for the dose-response relationship of fluticasone propionate was significantly higher from that for beclomethasone dipropionate, budesonide or triamcinolone acetonide.

Growth effects: For most children with mild to moderate asthma effective long term control may be attained using low doses of inhaled corticosteroids <400 microgram/day, that are not associated with any significant systemic bioactivity or effects on growth. Short term studies measuring lower leg length with knemometry have shown dose-related effects of inhaled corticosteroids. Three out of 6 medium and long term studies showed some reduction in measures of height with use of inhaled corticosteroids while the other three showed no effect.

Bone biochemical markers: All 9 studies showed some suppression of bone biochemical markers with inhaled corticosteroids.

Bone density: 2 of 6 studies showed no difference in bone density in those using corticosteroids, two studies showed a reduction in bone density mainly in women and two showed an overall reduction in bone density associated with inhaled corticosteroid use.

Effects of eyes, skin and leucocytes: results are not systematically presented.

Authors’ conclusions
Higher potency compounds such as fluticasone propionate may result in improved clinical efficacy, although this may be accompanied by a commensurate increase in systemic activity. Dose-response data shows that even when allowing
for differences in potency there is an excess of systemic activity with fluticasone propionate compared with other inhaled corticosteroids when therapeutically effective doses are compared. There are dose-related effects on bone metabolism using surrogate biochemical markers. Bone density measurements suggest an increased risk of osteoporosis and bone fracture related to cumulative exposure in susceptible patients receiving high-dose inhaled corticosteroid therapy. There is also evidence of a long-term accumulative effect for the development of posterior subcapsular cataracts.

CRD commentary
The review question is comprehensive and the authors search a number of electronic databases and conference proceedings for evidence. However, there is some restriction to English language publications and reference lists of retrieved studies are not searched which could result in some studies being missed. Inclusion criteria are stated but there is no information on how studies were screened for inclusion and validity assessment is not carried out. This leads to some difficulties in the presentation of the results as it is not possible to weight the studies in order of potential for bias. Although it seems appropriate to use narrative synthesis to present the results, given the diversity of participants, treatments and outcomes, more structure could have been used in their presentation. Some of the authors' conclusions seem to follow from the results, but should be treated with caution, given the above methodological limitations. Other conclusions (e.g. cataracts) may be based on expert opinion rather than systematic review of the evidence (it is unclear from the paper) and should be treated with more caution.

Implications of the review for practice and research
Practice: The authors state that bruising in the skin should prompt screening for other tissue-specific adverse effects. Growth should always be measured in any asthmatic child. For patients who require persistently high doses of inhaled corticosteroid regular annual or biennial checks should be made for effects on skin, eye, adrenal gland, bone and growth. Alternative non-steroidal treatments such as long-acting beta-2 agonists, theophyllines, cromones or antileukotrienes should be considered as a way of facilitating the use of lower doses of inhaled corticosteroid. The physician should strive to identify the lowest possible maintenance dose of inhaled corticosteroid because this will result in the smallest risk for long-term systemic effects. Post-menopausal women receiving high-dose inhaled corticosteroid therapy should be given oestrogen replacement therapy.

Research: The authors state that dose response studies to simultaneously evaluate anti-asthmatic efficacy and systemic activity are required in order to properly evaluate the relative therapeutic ratios of the different available inhaled corticosteroids. Further studies are required in high-risk groups other than post-menopausal women such as the elderly to evaluate the long-term effects of inhaled corticosteroids on bone density and fracture risk. Further data are needed on the risk of developing posterior subcapsular cataracts with high potency inhaled corticosteroids other than beclometasone (such as fluticasone).

Bibliographic details

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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.