A meta-analysis of the dose-response relationship of inhaled corticosteroids in adolescents and adults with mild to moderate persistent asthma

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Authors' objectives
To investigate whether inhaled corticosteroids (ICS) exhibit a dose-response relationship in the treatment of mild to moderate persistent asthma.

Searching
PubMed and MEDLINE were searched from January 1996 to January 2001 using the following search terms: 'asthma' and 'corticosteroids', 'glucocorticoids', 'beclomethasone', 'budesonide', 'fluticasone', 'flunisolide', 'mometasone' or 'triamcinolone acetonide'. The reference lists of the articles were also examined for other publications.

Study selection
Study designs of evaluations included in the review
The eligible studies had to be double-blind, randomised controlled trials (RCTs).

Specific interventions included in the review
ICS compared with a placebo. Studies had to examine at least two doses of the same ICS. Studies examining the discontinuation of oral corticosteroid therapy were excluded. The drugs examined in the analysis included fluticasone propionate, triamcinolone acetonide, budesonide and mometasone furoate. The doses ranged from 50 to 1,800 microg/day. Dose ranging studies were excluded.

Participants included in the review
Asthma. Adolescents and adults with mild to moderate persistent asthma were included. Studies of patients with severe asthma, or patients dependent on oral corticosteroids, were excluded. Trials that enrolled children aged less than 12 years were also excluded. The mean age of the patients in the included studies ranged from 26 to 51 years.

Outcomes assessed in the review
Five outcome measures were evaluated: the morning and evening peak expiratory flow rate (am PEFR and pm PEFR, respectively), the forced expiratory volume in one second (FEV1), the asthma symptom score, and the reported beta-antagonist use. The asthma symptom score was evaluated by patients using various scales to rate the severity of symptoms on a given day. Shortness of breath and night-time awakenings were excluded from the analysis.

How were decisions on the relevance of primary studies made?
The authors state that the abstracts of the articles were examined to identify relevant studies. They do not state how many of the reviewers performed the selection.

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

Data extraction
Two reviewers independently extracted the data. Detailed information on the clinical trials of interest was extracted from documents obtained from the US Food and Drug Administration. When relevant data could not be found, additional data were requested from the authors of the primary studies. The information tabulated in the review included: study identification, washout period, duration of treatment, doses, device (type of inhaler), number of patients, mean age, asthma severity, FEV1 cutoff, mean FEV1, and outcome data.
Methods of synthesis
How were the studies combined?
The authors conducted meta-regression analyses using Bayesian techniques to combine the data.

How were differences between studies investigated?
Heterogeneity was investigated using meta-regression analyses. To investigate the influence of the highest-dose groups, analyses of fluticasone and triamcinolone (the agents involved in the greatest number of trials) were undertaken in which the highest dose was omitted.

Results of the review
Sixteen RCTs with 4,703 participants were included in the review. There were 8 trials (n=2,227) of fluticasone propionate, 3 (n=1,337) of triamcinolone acetonide, 3 (n=597) of budesonide, and 2 (n=542) of mometasone furoate.

A statistically-significant dose response in am PEFR was observed with fluticasone propionate (95% confidence interval, CI: 4.9, 11.5), triamcinolone acetonide (95% CI: 4.7, 18.0) and budesonide (95% CI: 5.8, 24.9). A statistically-significant dose response to fluticasone propionate and triamcinolone acetonide was also observed in pm PEFR (95% CI: 2.0, 8.7 and 95% CI: 2.4, 13.7, respectively) and asthma symptom score (95% CI: -0.069, -0.002 and 95% CI: -0.60, -0.10, respectively). In terms of FEV1, the dose response was only statistically significant with budesonide (95% CI: 0.025, 0.17).

The relationships generally remained significant when analyses omitting the highest dose were conducted; the exception being the dose response in pm PEFR with fluticasone propionate, which was not significant.

Authors’ conclusions
Dose-response relationships were not uniformly observed with all of the drugs or for all of the response measures. Outcome measures, particularly am and pm PEFR, and to a lesser extent, FEV1, were sensitive to the dose of ICS. However, this effect was driven mainly by ICS doses below or at the low end of the recommended ranges, and not by the highest doses. The use of higher doses of ICS in patients with mild to moderate persistent asthma did not appear to increase the efficacy of these drugs.

CRD commentary
The review question and the inclusion and exclusion criteria were clearly stated. The authors searched MEDLINE and PubMed, which are almost identical, but do not appear to have searched for unpublished data. In addition, they do not state whether any language restrictions were applied, or justify why their search dates were relatively narrow. Thus, it is possible that some studies may have been missed, introducing retrieval bias. The validity of the individual studies does not appear to have been assessed.

The authors state that eligible studies were independently extracted by two reviewers. Sufficient details of the individual studies were tabulated, and the studies were summarised appropriately using a meta-regression. However, the authors’ conclusions presented in the abstract could have provided more information to clearly reflect the results and conclusions presented in the paper, i.e. where dose-response relationships exist (increasing the dose beyond a threshold value may provide little additional benefit in the alleviation of asthma symptoms).

The conclusions (as presented in the paper) appear to follow the results, but would be strengthened by including an assessment of the quality of the studies.

Implications of the review for practice and research
Practice: The authors state that therapeutic benefits can be maximised and adverse effects minimised by using the lowest effective ICS dose.

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