Dose response of inhaled corticosteroids in children with persistent asthma: a systematic review

Zhang L, Axelsson I, Chung M, Lau J

CRD summary

This review found that, compared with low doses, moderate doses of inhaled corticosteroids may not provide clinically relevant therapeutic advantages in children with mild-to-moderate persistent asthma. The unclear methodological quality of the included trials and the inclusion of a subset of the trials in the meta-analysis means the results should be interpreted with caution.«ST10.

Authors' objectives

To evaluate the relationship between dose and treatment response of inhaled corticosteroids in children with persistent asthma.

Searching

MEDLINE, The Cochrane Library (Issue 2, 2009) and DARE were searched to August 2009; search terms were reported. The clinical study register of GlaxoSmithKline was searched for unpublished studies. Reference lists of identified trials and systematic reviews were searched for additional studies.

Study selection

Randomised controlled trials (RCTs) of paediatric patients aged between three and 18 years with persistent asthma were eligible for inclusion. Trials had to administer inhaled corticosteroids in two or more different doses by the same delivery system for at least four weeks. At least one of the following outcome types had to be reported: efficacy outcomes; withdrawals due to lack of efficacy or adverse events; results from health-related quality of life questionnaires; airway inflammatory biomarkers; and/or safety outcome measures. The excluded were: crossover trials with a washout period of less than two weeks or no washout period, trials that compared single doses of inhaled corticosteroids with placebo or other interventions, and trials of mixed populations with no separate data reported for the paediatric patients.

The included studies were multicentre trials in 26 countries across five continents. All trials were sponsored by multinational pharmaceutical companies that manufacture inhaled corticosteroids. Moderate doses of inhaled corticosteroids were defined as 300 to 400μg per day; lower doses of corticosteroid were defined as 200μg or less of corticosteroid per day. Corticosteroids evaluated in the trials were fluticasone (by Diskhaler, dry-powder inhaler or Diskus), budesonide (by nebuliser, Turbuhaler or Diskhaler) hydrofluoroalkane, ciclesonide (by hydrofluoroalkane metered-dose inhaler), mometasone (by dry-powder inhaler) and beclomethasone (by hydrofluoroalkane Autohaler). Outcomes evaluated were peak expiratory flow for morning and evening, forced expiratory volume in one second (FEV_1), asthma symptom score and beta-2-agonist use. The analysis of adverse events included withdrawals due to lack of efficacy, oral candidiasis, dysphonia/hoarseness, cough and pharyngitis.

Two reviewers independently performed the study selection. Disagreements were resolved by consensus.

Assessment of study quality

Two reviewers independently assessed methodological quality of the included trials using The Cochrane Collaboration recommendations pertaining to six key domains of randomisation: allocation concealment, blinding method, descriptions of incomplete outcome assessment data, evidence of selective outcome reporting and evidence of other bias.

Any disagreements between the reviewers were resolved by consensus.

Data extraction

Data were extracted by one reviewer and confirmed by a second reviewer to calculate risk ratios (RR) and mean differences with 95% confidence intervals (CI) for each effect measure. Correction values were added in the event of

zero events. Intention-to-treat data were used where available. Any differences between the reviewers were resolved by consensus.

Methods of synthesis

Pooled risk ratios standardised mean differences (SMD), weighted mean differences and 95% confidence intervals were calculated using a DerSimonian and Laird random-effects model. Heterogeneity was assessed using I^2.

Sensitivity analyses were undertaken; two RCTs that measured as a percentage of predicated values rather than absolute values were excluded and the results of the meta-analysis to the Mantel-Haenszel and Peto methods of meta-analysis were compared. The authors planned to conduct subgroup analyses to explore sources of heterogeneity.

Results of the review

Fourteen RCTs (5,768 children) were included in the review. All trials were randomised with the use of double-blinding. Methods of randomisation were described in five trials. Allocation concealment was reported in one trial. There were nine placebo-controlled trials. Six trials used active comparators. Three trials had a duration of 52 weeks, 10 trials of 12 weeks duration and one trial 54 weeks.

There were statistically significant benefits observed with moderate doses of inhaled corticosteroids in FEV_1 (SMD 0.11, 95% CI 0.01 to 0.21; six trials; 1,601 children) compared with low doses. Moderate, non significant benefits were observed in peak expiratory flow in the morning and evening, asthma symptom scores, and the requirement for beta-2-agonist use. No statistically significant heterogeneity observed across the trials except for beta-2-agonist use (I^2=65%). There were no differences between moderate and low dose regimens in withdrawals due to lack of efficacy.

There were no significant differences observed between low and moderate doses of inhaled corticosteroids on linear growth (two trials) or on local adverse events and withdrawal due to adverse events.

The most common adverse event was pharyngitis/sore throat (overall rate 7.7%). Some heterogeneity was observed by dysphonia/hoarseness (I^2=39%).

Planned subgroup analyses were not performed because of the small numbers of included trials. The sensitivity analysis using three different statistical models found similar results.

Authors' conclusions

Current evidence was insufficient to define the dose-response relationship in children with mild to moderate persistent asthma. Moderate doses of inhaled corticosteroids may not provide clinically relevant therapeutic advantages in this population.

CRD commentary

The review addressed a clear question. Criteria for the inclusion of studies were defined. Appropriate databases were searched and attempts were made to identify unpublished literature. There were language limitation; the authors acknowledged one trial that was not included for this reason. Steps were taken to limit bias and errors at each stage of the review process.

Methodological quality was assessed, but not all the results of this assessment were published so the outcome remained unclear. Few of the trials reported methods of randomisation. The authors reported that the risk of bias was unclear for most trials. The authors acknowledged the limitations of the review due to the unclear methodological quality of the included trials, the heterogeneity in severity of asthma, and potential biases because less than half of the included trials were used in the meta-analysis.

Given that the authors' conclusions are based on a subset of the included trials, the results of the review should be interpreted with some caution.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that additional high quality trials were required to compare efficacy and safety of

different doses of inhaled corticosteroids in children with persistent asthma, particularly higher dose ranges in patients with more severe asthma. Future trials require stratified randomisation to ensure comparability in dose groups for asthma severity and baseline corticosteroid use.

Funding
CAPES, Brazil.

Bibliographic details
Zhang L, Axelsson I, Chung M, Lau J. Dose response of inhaled corticosteroids in children with persistent asthma: a systematic review. Pediatrics 2011; 127(1): 129-138

PubMedID
21135001

DOI
10.1542/peds.2010-1223

Original Paper URL
http://pediatrics.aappublications.org/content/127/1/129.abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Administration, Inhalation; Adolescent; Adrenal Cortex Hormones /administration & dosage; Asthma /drug therapy; Child; Child, Preschool; Dose-Response Relationship, Drug; Humans; Randomized Controlled Trials as Topic

AccessionNumber
12011000616

Date bibliographic record published
28/09/2011

Date abstract record published
19/03/2012

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.