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[Intervention Review]

Beclomethasone for asthma in children: effects on linear growth

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ABSTRACT

Background

Inhaled steroids play a central role in the management of childhood asthma. There is concern about their side effects, especially on growth. However asthma may also cause growth retardation. Growth rates are not stable, so randomised controlled parallel group studies are needed to assess the impact of inhaled steroids on growth. This review is confined to one inhaled steroid, beclomethasone, that is known to have significant levels of systemic absorption.

Objectives

To determine whether inhaled beclomethasone cause significant delay in the linear growth of children with asthma.

Search methods

The Cochrane Airways Group asthma register was searched. Bibliographies from included studies, and known reviews were searched for additional citations. Personal contact with colleagues and researchers working in the field of asthma were made to identify potentially relevant trials.

Selection criteria

Randomized, controlled trials comparing the effects of beclomethasone to non-steroidal medication (placebo or non-steroidal therapy) on the linear growth of children with asthma.

Data collection and analysis

Data related to the clinical outcome "change in growth" were extracted by two reviewers working independently

Main results

One hundred and fifty-nine citations were identified by the search strategy and bibliography review. Three studies met the inclusion criteria. All used beclomethasone 200 mcg twice daily delivered by dry powder Diskhaler to treat children with mild-moderate asthma. Study duration was 7-12 months. In all three studies, a significant decrease in linear growth occurred in children treated with beclomethasone compared to those receiving placebo or non-steroidal asthma therapy. The average decrease, calculated through meta-analysis, was -1.54 cm per year (95% CI -1.15, -1.94).

Authors' conclusions

In children with mild-moderate asthma, beclomethasone 200 mcg twice daily caused a decrease in linear growth of -1.54 cm per year. These studies lasted a maximum of 54 weeks, so it remains unclear whether the decrease in growth is sustained or whether it reverses

with 'catch up' after therapy is discontinued. We are unable to comment on growth effects of other inhaled steroids that have potentially less systemic effects. If inhaled steroids are required to control a child's asthma, we recommend using the minimum dose that effectively controls the child's asthma and closely following growth.

PLAIN LANGUAGE SUMMARY

The effect of beclomethasone on height in children

During an asthma attack, the airways (passages to the lungs) narrow from swelling (inflammation) and muscle spasm. This causes breathing problems, wheezing and coughing. Inhaled steroids are used to reduce the swelling to the airways, but they may also stunt growth in children. The review of trials found that the inhaled steroid, beclomethasone causes an average decrease in growth of about one and a half centimetres a year. However, it is not known whether there is any catch-up growth once the treatment is stopped. More research is needed.

BACKGROUND

The important role of the inflammatory process in the etiology of asthma is clearly recognized in recent consensus statements from the National Heart, Lung and Blood Institute of the National Institutes of Health (USA), the British Thoracic Society, Japanese Society of Allergy, Canadian Thoracic Society, South African Pulmonology Society, and the Thoracic Society of Australia and New Zealand ([Nat Inst Health 1997](#), [British Thor Soc 1993](#), [Japan Soc All 1995](#), [Beveridge 1996](#), [S African Pulm 1992](#), [Woolcock 1993](#)). This belief is based in part on studies revealing significant improvement in asthma outcomes when patients were treated with inhaled or systemic steroids ([Barnes 1993](#), [Dahl 1993](#), [Fabbri 1993](#), [Gustafsson 1993](#), [Haahtela 1991](#), [Jeffery 1992](#), [Rafferty 1985](#), [V Essen-Zand 1992](#)). Inhaled corticosteroids are now felt to be the most effective long-term maintenance therapy available for mild, moderate, or severe persistent asthma. As a result they are recommended for all children with moderate or severe asthma and are recommended for consideration in children with mild persistent asthma as well.

As with all therapeutic interventions, there are benefits and risks to the use of inhaled steroids in children with asthma. Benefits include the substantial improvement in all measurable asthma outcomes in children treated with inhaled steroids. Risks, though less well studied, may include altered hypothalamic-pituitary axis functioning ([Boorsma 1996](#), [Brown 1993](#), [Clark 1996](#), [Prahl 1991](#), [Tabachnik 1991](#)) and delayed linear growth ([Tinkelman 1993](#), [Doull 1995](#), [Simons 1997](#), [Allen 1994](#)). The recent requirement by the Food and Drug Administration of the U.S. Department of Health and Human Services to require labelling on all inhaled and intranasal corticosteroids warning of a possible reduction in linear growth in children well depicts this concern (FDA 1998). Attempts to determine the effect of inhaled steroids on linear growth in children with asthma are confounded by the facts that children with poorly controlled asthma tend to be growth delayed, have longer periods of reduced growth rates prior to puberty, reach puberty later than non asthmatics, and often require intermittent systemic steroids which are known to cause growth delay ([Allen 1996](#), [Balfour-Lynn 1986](#), [Kamada 1995](#)). The one previous attempt to systematically evaluate the literature describing the effect of inhaled steroids on the linear growth of children with asthma, a meta-analysis by Allen ([Allen 1994](#)), had several flaws. In addition, several studies of high methodological quality released since this meta-analysis conflict with its conclusions ([Tinkelman 1993](#), [Doull 1995](#), [Simons 1997](#)).

In summary, the existence of multiple studies with conflicting results, weaknesses of the only published meta-analysis, and the persistent uncertainty in both clinical and research sectors as to whether any or all inhaled steroids cause significant linear growth delay in children with asthma, led us to undertake this systematic review.

OBJECTIVES

To determine whether steroids delivered by nebulizer, metered-dose inhaler (MDI), diskhaler, rotahaler, or turbuhaler cause significant delay in the linear growth of children with asthma

METHODS

Criteria for considering studies for this review

Types of studies

To be included in the review, studies had to be randomized, single or double-blind, controlled trials comparing the use of beclomethasone with either placebo or non-steroidal medication in children with asthma.

Types of participants

Children (<18 years old at entry into the study) with the diagnosis of asthma, who have been off inhaled and oral steroids for a minimum of 3 months prior to the study.

Types of interventions

Patients must have been participants in studies that utilize randomization to assign beclomethasone, or a non steroidal medication (control). The inhaled steroid must have been delivered by a nebulizer, metered-dose inhaler, diskhaler, or rotahaler for a minimum of 3 months. All doses were accepted, and were classified into the categories of 'low', 'medium', or 'high' as defined by the United States NHLBI guidelines ([Nat Inst Health 1997](#))

Types of outcome measures

Primary outcomes

The primary outcome measure was linear growth velocity. All studies including outcomes that could be converted to linear growth velocity were considered.

Search methods for identification of studies

Electronic searches

The Cochrane Airways Group asthma register was searched using the following terms:

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((steroid* OR corticosteroid* OR glucocorticoid* OR
beclomethasone) AND (inhale*)) AND (child* OR infan* OR
adolescen* OR pediater* OR paediatr*)
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Each abstract was reviewed and annotated as: randomized controlled trial (RCT), clearly not an RCT or unclear. Only publications annotated as clearly not an RCT were removed at that stage.

Searching other resources

Each remaining abstract from the search results was reviewed to determine if it met the inclusion criteria. Trials with citations having relevant titles not displaying abstracts were reviewed to determine eligibility, as were all trials not specifically removed for failure to meet the inclusion criteria based on title or abstract. Reference lists of all identified RCTs were checked to identify potentially relevant citations. Personal contact was made with colleagues and researchers working in the field of asthma to identify potentially relevant trials.

Data collection and analysis

Selection of studies

From the title, abstract, or descriptors, two reviewers (PS and DB) independently reviewed literature searches, bibliographies, and texts to identify potentially relevant trials for full review. From the full text, two reviewers (PS and DB) independently selected trials for inclusion into this review based on the inclusion criteria. Agreement was measured using Kappa statistics, and disagreement was resolved by consensus.

Data extraction and management

Data for the trials were extracted by two reviewers (PS and DB). Primary study authors were contacted to provide additional clarification and information for the review if necessary. Confirmation of methodology and data was obtained in one study (Doull 1995). A second study (Simons 1997) required an estimate of standard deviations from other data presented in the paper as the authors could not be contacted.

Assessment of risk of bias in included studies

Methodologic quality assessment: Each reviewer independently assessed the methodological quality of the included trials and ranked them using the Cochrane approach to quality assessment (Mulrow 1997) based on allocation concealment (randomization) as follows:

Grade A: Adequate allocation concealment

Grade B: Uncertain

Grade C: Clearly inadequate allocation concealment

Inter-rater reliability was measured by using simple agreement and kappa weighted statistics. Where there was uncertainty, authors were contacted to clarify the allocation concealment (randomization) method used.

In addition, each author independently assigned a quality score based on the methodology of Jadad (Jadad, 1996) to each included study. With this methodology, each study included is assessed using a 0-5 scale as summarized below:

1. Was the study described as randomized (1=yes; 0=no)?
2. Was the study described as double blind (1=yes; 0=no)?
3. Was there a description of withdrawals and dropouts (1=yes; 0=no)?
4. Was the method of randomization well described and appropriate (1=yes; 0=no)?
5. Was the method of double-blinding well described and appropriate (1=yes; 0=no)?
6. Deduct 1 point if methods for randomization or blinding were inappropriate.

Measures of treatment effect

Linear growth velocity was analysed as a continuous variable, so individual and pooled statistics were calculated as weighted mean differences (WMD) and 95% confidence intervals. A fixed effects model was used

Data synthesis

For analysis, data were entered into RevMan to ensure that the Cochrane convention was followed: i.e. that differences between

treatments that favoured control went to the left, and those favouring treatment went to the right. In this review, the outcome (growth velocity) was reduced (unfavourably) by the treatment - thus favouring control.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was planned a priori to compare the effect on linear growth of specific strengths of inhaled steroid used (low, medium, or high).

Sensitivity analysis

Six specific sensitivity analyses were planned a priori. These analyses were planned to evaluate the role of each of the following in the final statistical summary:

1. The random effects compared to fixed effects model
2. High methodologic compared to low methodologic quality studies
3. Published compared to unpublished data (publication bias)
4. Duration of intervention (less than six months compared to greater than six months)
5. Age of subjects (less than 13 years of age compared to greater than 13 years of age)
6. Method of delivery of inhaled steroid (nebulizer compared to metered-dose inhaler compared to rotahaler compared to turbuhaler compared to diskhaler)

RESULTS

Description of studies

Results of the search

A total of 159 citations were identified using both the search strategy described above and bibliography review. The search strategy identified 93 citations, and the bibliography review identified 66 additional citations. Sixty-seven citations were eliminated by review of the title or abstract with the remaining 92 citations being reviewed with full text. Of these 92 remaining citations, 3 studies satisfied all eligibility requirements for inclusion and 89 studies did not. Reasons for study exclusion included: improper study design (n=113), improper population (n=19), improper outcome measure (n=9), improper intervention (n=8), improper control group (n=3), and the study used a subset of a larger population published in total elsewhere (n=4). Substantial inter rater agreement (K score, 0.98) for trial inclusion into the meta-analysis for the studies not excluded by title or abstract was attained (Last 1995).

Included studies

Only three studies met the inclusion criteria: Doull 1995, Verberne 1997, and Simons 1997. All of these studies used the inhaled steroid beclomethasone.

Design: Each of the included studies was a randomized controlled clinical trial. Each was double blind (subject and provider) to treatment assignment.

Populations: Although all studies required study patients to have asthma, they differed substantially on their definitions. Two studies [Verberne 1997, Simons 1997] used pulmonary function test requirements for inclusion, while the third study [Doull 1995] did not. One study (Doull 1995) required a minimum symptom burden while the other two [Verberne 1997, Simons 1997] did not. Each study selected a population of patients thought to have clinically stable asthma at the time of enrolment, and each selected a population consistent with the mild to moderate category of asthma as defined by the NIH guidelines (Nat Inst Health 1997). Each study enrolled only patients that had been off of inhaled or systemic steroids for a minimum of 3 months (Doull 1995: never used steroids; Verberne 1997: no steroids for at least 6 months; Simons 1997: no steroids for at least 3 months and sum total of steroids was less than 1 month). Drop out rates varied widely between studies (Doull 10.6%; Verberne 16.1%; Simons 25.3%)

Interventions: Each of the three studies used beclomethasone. Two of the three [Verberne 1997, Simons 1997] used a diskhaler device for delivery while the third [Doull 1995] used a metered-dose inhaler. Two of the three [Doull 1995, Simons 1997] used a placebo control while the third [Verberne 1997] used Salmeterol as the control medication. The dose of beclomethasone was consistent between all three studies at 200 mcg twice daily which is classified as medium dose by National Asthma Education and Prevention Program Expert Panel Report II: Guidelines for the Diagnosis and Management of Asthma (Nat Inst Health 1997). The duration of treatment varied from 7 months [Doull 1995] to 54 weeks [Verberne 1997]. Compliance was estimated in two of the studies [Doull 1995, Verberne 1997] ranging from 75% to 92%.

Outcome: All three studies reported changes in height for the duration of the treatment, and calculated growth velocity using the regression coefficient of height on time. One study [Simons 1997] did not report the standard deviations for the linear growth velocities of each group and attempts to obtain this information from the author were unsuccessful. From data provided in the text, standard deviations were estimated using the assumption that the standard deviation of intervention and control groups was equal. This is a reasonable assumption that does not significantly alter the results of the meta-analysis. Two of the three studies [Verberne 1997, Simons 1997] used a stadiometer to measure height while the third study [Doull 1995] used a minimeter. Only one of the three trials [Doull 1995] used growth as the primary outcome. In the other two [Verberne 1997, Simons 1997] growth was recorded as a secondary outcome measure.

Risk of bias in included studies

Randomization: All included studies allocated treatment by randomization. Two studies used an independent randomization center [Doull 1995, Verberne 1997]. The third study [Simons 1997] does not discuss how randomization was accomplished and attempts to contact the authors were unsuccessful.

Blinding of treatment and outcome assessment: All studies are described as double-blind. The measurer of height was blind to the treatment group in one study [Doull 1995], but measurer blindness is not stated in the other two studies [Simons 1997, Verberne 1997].

Exclusion after randomization: Drop out rates varied from 10.6% [Doull 1995] to 16.1% [Verberne 1997] to 25.3% [Simons 1997]. Each

study adequately addressed the reasons for drop out. In order of frequency these included: severe asthma exacerbation during the study, adverse events, noncompliance with the protocol, control patients initiating inhaled steroids, back injury affecting growth, and "other". Only one study [Doull 1995] used an intention to treat analysis which revealed similar conclusions when the dropouts were included or excluded in the analysis.

Effects of interventions

The weighted-mean difference from the meta-analysis was -1.54 cm per year (95% confidence interval -1.15, -1.94). This corresponds to a reduction in growth velocity of approximately 25%.

Subgroup analysis comparing the effects of different dosing levels of inhaled steroids (low, medium, or high) was not possible since beclomethasone was used in 200 mcg twice daily was used in all three studies.

Sensitivity analysis of the affects of the statistical model (random effects vs. fixed effects), methodological quality, publication bias, duration of intervention (less than 6 months versus greater than 6 months), age of subjects (less than 13 years old versus greater than 13 years old), and method of delivery of inhaled steroid (nebulizer versus MDI versus rotahaler versus turbuhaler versus diskhaler) were performed. The results are summarized below.

Random vs. fixed effect model: Use of the random effects model with our included studies reveals a weighted mean difference of -1.51 cm/year and a confidence interval of (-1.03, -1.99). This outcome is consistent with that of the fixed effect model which calculates a weighted mean difference of -1.54 cm per year and confidence interval of -1.15 cm per year to -1.94 cm per year.

Methodologic Quality: Quality scores were calculated using two separate formulas. Assessment based on allocation concealment (Mulrow 1997) revealed two studies with grade A [Doull 1995, Verberne 1997] and one study with grade B [Simons 1997]. Assessment, based on the method of Jadad (Jadad 1996), resulted in a grade of 5 for one study [Doull 1995], grade 4 for one study [Verberne 1997] and grade of 3 for the third [Simons 1997]. Each study was evaluated independently for quality by the two authors, with Kappa scores of 1.0 for allocation concealment and 1.0 for the method of Jadad. Removal of all studies of lower quality (less than grade A concealment allocation) resulted in a weighted mean difference of -1.73 cm per year (95% CI -1.27, -2.20). Similarly, removal of all studies of lower quality with Jadad score less than 4 again resulted in a weighted mean difference of -1.73 cm/year (95% CI -1.27 to -2.20).

Publication Bias: A funnel plot showed no evidence of publication bias.

Length of treatment: Since none of the studies included was less than 6 months duration, no sensitivity analysis could be performed based on this criterion.

Age of subjects: Sensitivity analysis of subjects based on age (below or above 13 years old) could not be performed due to an inability to accurately group patients by age. Authors were unable to provide individual data stratified by age.

Mode of medication delivery: Since all three studies [Simons 1997, Verberne 1997, Doull 1995] used diskhalers, no sensitivity analysis could be performed on this criterion

There was no heterogeneity between studies; chi square was 2.71 with 2 degrees of freedom >.99.

DISCUSSION

Three studies evaluating the effect of inhaled steroids on the linear growth of children with asthma met our inclusion criteria. Although each population had mild to moderate asthma severity, important differences in study interventions and populations existed that might have influenced the results of this analysis. First, the duration of steroid therapy varied between studies with a minimum of 7 months [Doull 1995] to a maximum of 54 weeks [Verberne 1997]. Second, the inclusion criteria for subjects differed between studies. No attempts were made in any of these studies to classify patient severity based on the internationally recognized guidelines. Only two of the studies [Simons 1997, Verberne 1997] incorporated pulmonary function test parameters into the inclusion criteria. Each study used a different baseline between the last use of inhaled steroid allowed and enrolment (from "three months" before the study to "never allowed"). Third, the total number of analysed patients varied from 67 [Verberne 1997] to 241 [Simons 1997]. Finally, drop out rates varied between studies, from 10.6% [Doull 1995] to 25.3% [Simons 1997]. The impact of all of these differences is unknown, however the similar effect sizes and absence of heterogeneity suggest that their impact was small.

The meta-analysis shows a statistically significant decrease in linear growth velocity of children with mild to moderate asthma treated with moderate doses of beclomethasone. This is the opposite conclusion that reached by Allen et al in their meta-analysis of observational studies [Allen 1994]. Several reasons for this discrepancy are plausible. First, to minimize selection bias we only used randomized controlled trials whereas Allen et al used only cohort studies. Second, to promote equivalent control and study populations, the control population groups in the studies included in this review only contained children with asthma whereas Allen et al allowed control populations of children without asthma. Third, we used an extensive search strategy to minimize study selection bias whereas Allen et al did not state their search strategy. Fourth, we included studies that either measured growth velocity directly or had outcomes that could be converted to growth velocity. In contrast, Allen et al excluded all studies using growth velocity or summary statistics in the outcome. Fifth, we graded the quality of each included study and performed sensitivity analysis to determine the effect of study quality on the outcome measure, whereas Allen et al did not. Sixth, although not an a priori exclusion criterion, all studies included in our analysis had loss to follow up at 25% or less whereas Allen et al included studies with much larger loss to follow-up. Seventh, we evaluated the effects of publication bias on the overall conclusions of the meta-analysis whereas Allen et al did not. Finally we tested the effect of heterogeneity of the effect sizes between studies, whereas Allen et al did not statistically determine the possibility of significantly heterogeneous study populations. Overall, we conclude that methodologic rigor of our analysis increased the reliability of our findings and the conclusions to be drawn from them.

A review of the Hill criteria for causal inference [Hill 1965], strengthens our conclusion that 200 mcg twice of beclomethasone

causes decreased linear growth in children with mild to moderate asthma. First, the quality of the included trials was high, since all were all randomized controlled clinical trials that passed a set of a priori inclusion criteria. Second, the size of the measure of effect is large and of clinical significance. Third, the effect of inhaled steroids on linear growth is consistent across all three trials, despite a variety of ages, ethnicity, and treatment duration. Fourth, there is substantial indirect evidence that supports the likelihood that inhaled steroids effect linear growth. Studies evaluating inhaled steroids have shown decreased bone formation in adults [Ali 1991, Toogood 1991, Pouw 1991, Packe 1992], systemic steroids are well-known to cause significant growth delay [Allen 1996, Balfour-Lynn 1986, Kamada 1995], inhaled steroids have been shown to depress the hypothalamic-pituitary axis revealing significant systemic absorption [Boorsma 1996, Brown 1993, Clark 1996, Prahl 1991, Tabachnik 1991], and recent data suggests nasal steroids may effect growth velocity [FDA 1998]. Fifth, plausible alternative explanations of the observed effects, including selection bias and publication bias, have been minimized or eliminated by the methodology of this review. The sixth and final criterion for causal inference, that of a dose-response relationship between inhaled steroids and linear growth delay could not be evaluated because all studies used the same dose of drug.

We could not carry out sensitivity analysis of subjects based on age (below or above 13 years old). Two of the studies, [Simons 1997, Verberne 1997] included patients above and below age 13, but analysis within the publication was not stratified into these age groups. Authors were unable to provide individual data stratified by age. This is of interest since there is evidence that inhaled steroids may not effect linear growth in post-pubescent adolescents [Tinkelman 1993].

The effect of removing studies utilizing different methods of medication delivery was minimal. Two studies [Simons 1997, Verberne 1997] used Diskhalers for the delivery of treatment and control medication, while the third [Doull 1995] used metered-dose inhalers. Within the limits of the available evidence, we conclude that the mode of medication delivery does not significantly alter the effect of beclomethasone on growth.

Finally, we are not able to comment on the possible effects on growth of other inhaled steroids that may have lower levels of systemic activity, nor on the impact of alternative systems for the delivery of corticosteroids.

AUTHORS' CONCLUSIONS

Implications for practice

Beclomethasone 200 mcg twice daily in children with mild to moderate asthma significantly reduces linear growth velocity over 7-12 months in children with mild to moderate asthma. It is not known whether similar effects occur with other inhaled steroids such as budesonide or fluticasone that have lower systemic bio-availability. It is not known whether there is significant catchup growth if the beclomethasone is discontinued. These data suggest that inhaled steroid use be kept to the smallest dose that adequately controls the disease. It would seem prudent to use an inhaled steroid with potentially less systemic effect than beclomethasone. Regular monitoring of linear growth in children with asthma using these medications may aid treatment decisions in individual patients.

Implications for research

Research efforts should concentrate on evaluating the long-term effects of inhaled steroids, effects of other inhaled steroid medications, and the effect of different doses. If growth effects are unavoidable with maintenance treatment, dosing strategies that may permit catch up periods should be evaluated.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Doull 1995

Methods	Randomized, double blind, clinical trial
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Doull 1995 (Continued)

Participants	Age 7-9 years, replied to questionnaire, > or = 5 wheezing episodes in past year OR wheeze exacerbation lasting > or = 3 days in past year. Exclusion criteria: use of inhaled steroids (ever), use of systemic steroids (ever), severe respiratory distress
Interventions	7 months of placebo or MDI Beclomethasone at 200 micrograms BID
Outcomes	Intervention group: Linear growth of 4.12 cm/yr Placebo group: Linear growth of 5.94 cm/yr
Notes	Asthma severity= mild (definition not stated)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Simons 1997

Methods	Randomized, double blind, placebo controlled, clinical trial
Participants	Ages 6-14 years, clinically stable asthma, less than 1 month inhaled or systemic corticosteroids ever, no steroids >3 months prior to study, FEV1 > 70 6 hours after B agonist held, 10% increase FEV1 30 minutes after B agonist, <8mg methacholine to decrease FEV1 20%, ability to refrain from study meds for 36 hours, ability to stop albuterol 6 hours prior to visit Exclusion criteria: ER/hosp in last 3 months, Hx life threatening asthma, hx life threatening reaction to study meds in the past
Interventions	Intervention: Beclomethasone 200 micrograms BID via diskhaler for 1 year Group 2: Serevent 50 micrograms BID via diskhaler for 1 year Placebo (lactose): 1 puff BID via diskhaler for 1 year
Outcomes	Intervention: 3.96 cm/year growth Group 2: 5.40 cm/year growth Placebo: 5.04 cm/year growth
Notes	Standard deviations of treatment and control groups assumed to be equal, then calculated based on data reported in text of publication. Authors unable to be contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Verberne 1997

Methods	Randomized, double-blind, controlled
Participants	6 years-16 years old, mild-moderate asthma, chosen from outpatient clinic of 6 university hospitals and 3 general hospitals, FEV1 55-90% or FEV1/FVC 50-75%, increase FEV1 > 10% with .8mg salbutamol, de-

Verberne 1997 *(Continued)*

crease FEV₁>20% after 150 micrograms methacholine, ability to produce reproducible lung fxn tests as determined by <5% variation on 3 consecutive FEV₁, hx stable asthma>1 mo without exacerbations or respiratory tract infxns, no inhaled steroids for >6 months, no cromoglycate>2 weeks

Interventions	Beclomethasone rotadisk/diskhaler 200micrograms BID Salmeterol rotadisk/diskhaler 50 micrograms BID for 1 year
Outcomes	Intervention: 4.70 cm/year growth Control: 6.10 cm/year growth
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agertoft 1994	not an RCT
Ahrens 1993	review
Allen 1998	only 2 weeks ramp up time
Apold 1975	not a clinical trial
Arkins 1968	adults
Bennati 1989	only 4 weeks inhaled steroid
Benoist 1992	editorial
Bisgaard 1990	Not an asthma trial
Bisgaard 1993	only 4 weeks inhaled steroid
Boner 1995	length not measured
Booms 1997	adults
Clark 1996	only 4 weeks inh steroid
Crowley 1995	not a clinical trial
Crowley 1998	not an RCT
Damsbo 1994	adults

Study	Reason for exclusion
De Blic 1996	no ramp up off inh steroids
Doull 1995(2)	only 1 day inh steroids
Doull 1996	Subpopulation of included study
Doull 1997	Subpopulation of other trial
Droszcz 1988	adults
Du toit 1986	Adults
Eefthimiou 1998	Review
Falliers 1982	only 4 weeks inh steroid, length not an outcome
Field 1982	no ramp up time, inhaled steroid controls
Francis 1984	only 8 weeks inhaled steroid, length not an outcome
Frank-Piskorska 1988	adults
Freezer 1995	length not an outcome
Galant 1996	ramp up time less than 1 month
Ggajanan 1993	only 2 weeks inhaled steroid
Haahtela 1991	length not an outcome
Henriksen 1985	inh steroid only 3 weeks, length not an outcome
Hoekstra 1996	length not an outcome
Horn 1990	not an RCT
Ishihara 1995	not an RCT
Jones 1994	length not an outcome
Joubert 1985	only 1 dose inh steroid
Kerstjens 1994	only 4 weeks inh steroids
Kerstjens 1995	adults, length not an outcome
Kolaczowska 1996	not an RCT
Kudo 1995	adults
Laviolette 1994	adults
MacKenzie 1998	review
Maestrelli 1993	adults

Study	Reason for exclusion
Mahajan 1997	subgroup of included study
Malka 1994	review
Malo 1996	adults
Merkus 1993	only 2 weeks ramp up with steroid free
Moller 1996	adults
Nathan 1997	only 4 weeks inhaled steroid
Nyholm 1984	adults
Overbeek 1996	adults
Pearlman 1997	no ramp up time off steroids, length not an outcome
Pedersen 1996	length not an outcome
Pepys 1975	not a clinical trial
Ponticiello 1997	adults
Price 1997	inhaled steroid controls
Prieto 1994	not an RCT
Reid 1996	not an RCT
Riordan 1974	only 2 weeks inh steroid
Roisman 1995	adults
Sheffer 1996	length not an outcome
Smith 1987	review
Sparkes 1974	not an asthma trial
Storr 1986	inhaled steroid controls
Sutochnikova 1996	adults
Taskar 1993	only 4 weeks inh steroid
Taylor 1975	only 8 weeks inh steroid
Tinkelman 1993	Ramp up time only 1 month
Todd 1997	letter
Toogood 1987	steroid controls
Toogood 1991	only 4 weeks inhaled steroid

Study	Reason for exclusion
Trigg 1994	adults
Van Essen-Zand 1986	only 8 weeks inhaled steroid
Van Essen-Zand 1992	only 2 weeks ramp up time
Van Essen-Zand 1994	not a RCT
Van Essen-Zandv 1995	subpopulation of included article
Waalkens 1993	length not an outcome
Wang 1994	adults
Wasserman 1996	ramp up time less than 1 month off inh steroids
Webb 1986	not an asthma trial
Wennergren 1996	not an RCT
Wilken-Jensen 1975	not a clinical trial
Wilson 1995	not an asthma trial
Wolfe 1996	length not an outcome
Wolthers 1995	letter
Wong 1992	only 15 days inh steroid, length not an outcome
Wyatt 1978	not a clinical trial
Yazigi 1978	only 1 day inhaled steroid

DATA AND ANALYSES

Comparison 1. Inhaled Steroid vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Linear growth velocity	3	273	Mean Difference (IV, Fixed, 95% CI)	1.54 [1.15, 1.94]

Analysis 1.1. Comparison 1 Inhaled Steroid vs placebo, Outcome 1 Linear growth velocity.

FEEDBACK

An alternate evaluation of evidence: results from a CASP workshop, 29 April 2011

Summary

In 2010 paediatric hospital professionals attending an EBM workshop held in Rome critically appraised this systematic review (SR). To do so they compared the acknowledged Critical Appraisal Skill Programme (CASP) tool with an unpublished strategy developed in Ulm University, Evidence-Based Knowledge Brokering (EBKB), appraising only the two weighted RCTs in the forest plot.

When participants used the CASP, they found good internal validity (clear research question, detailed search strategy, right studies included, appropriate assessment and statistical analysis). Answering the question on external validity, participants could not tell whether the results applied to the local population, especially given baseline differences in pre-study inhaled corticosteroid treatment (from no prior steroid treatment permitted, to stipulating a pre-treatment exposure of 3 months before the study). Even though the Cochrane review authors suggested these differences had scarce influence on outcome, given similar effect sizes and low heterogeneity (I²=26%), workshop participants were sceptical about differences in asthma severity and brief follow-up.

With the EBKB strategy, despite a clearly stated research question, workshop participants identified major limitations rating internal validity as poor. For example, they identified possible publication bias with the exclusion of long-term prospective studies needed to answer the research question (Sinha et al. 2008). The authors also neglected possible risk distribution from age-related changes including children 6 to 16 years, the typical age for constitutional growth delay, overweight children and children in different pubertal stages at baseline (selection bias). Because severity scores for asthmatic children were assessed differently in the two RCT studies, workshop participants suspected a type I error, and attrition bias from the numerous patients lost to follow-up. Participants also questioned including the study by Simons et al. because allocation concealment was unclear and the review authors did not contact the authors to clarify this. Appraising the longitudinal study by Doull et al., workshop participants considered the research question clear, but in excluding children using oral or inhaled corticosteroids the investigators failed to specify other possible routes and timing. Furthermore the review authors did not specify whether this population had received corticosteroids in before study-entry. Despite saying why Doull et al. excluded 10 children, the review authors considered all 94 children but did not provide an intention-to-treat analysis. Our participants suspected that removing the data for 6 children at a mean age of 8.5 years (pubertal development, inhaled corticosteroids, back injury) might have introduced selection bias from adverse events, for example iatrogenic precocious puberty, attributable to unspecified systemic corticosteroid therapy (Leone et al 2003; Leong et al 2007). Nor did the study provide information on overweight, children's bone age (Epstein et al. 1985; Preece 1988; Spadoni and Cianfarani 2010), and bone turnover (Baxter-Jones 2002). Given the similar adrenal function test findings (urinary cortisol) in Doull et al.'s study, participants suspected that the significant result in the linear growth regression analysis (SD 2.66 versus 3.66 cm CI -1.36 to -0.64) was a possible type I error.

Using the EBKB strategy, workshop participants also appraised Verberne et al.'s study. Because corticosteroid-related changes in height were considered only as a secondary outcome (adverse events), although the population included pubertal children (6 to 16 years), no information was provided on baseline characteristics for pubertal development, bone age and pubertal stages (clinical/x-ray/hormonal tests). Hence participants suspected that the significant linear growth decrease might be a transient effect ultimately followed by catch-up growth (Lipworth 1999). In assessing external validity, participants concluded that these shortcomings prevented them from generalising the findings to the local population.

In conclusion, the new EBKB appraisal strategy provides useful feedback that might help the review authors to reconsider their recommendations, elucidate uncertainty around corticosteroid doses and update this SR of intense interest to health professionals caring for children with asthma.

Summary of the evidence-based knowledge brokering (EBKB) strategy used for appraising systematic reviews (SRs)

First step Check whether the research question in the last paragraph in the introduction is clearly stated. If yes, complete the following five steps; if no, suspect poor internal validity.

Second step Check which method you consider simple and appropriate for answering the stated research question.

Third step Identify two or more major randomised controlled trials (RCTs) (high weight in the SR forest plot)

Fourth step Read the methods section. Read details of the two RCT populations (Table 1 in the RCT) and say whether you consider the population and study setting appropriate for comparison with the control group, for example similar risk profiles, and patients' demographic characteristics.

Fifth step Say whether you consider the statistical tests adequate for answering the question, for example, whether the study group and control group had the same risk distribution.

Final step

Express finally an opinion on whether the answer to the research question was clinically relevant and whether the study is valid to be included in the SR.

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Reply

This review is no longer being updated. It is being replaced by three new protocols evaluating the effect of inhaled steroids on growth. The unabridged version of this feedback has been sent to the authors of the new protocols.

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Beclomethasone for asthma in children: effects on linear growth (Review)

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WHAT'S NEW

Date	Event	Description
8 July 2011	Amended	Reference amended in feedback.

HISTORY

Protocol first published: Issue 2, 1998

Review first published: Issue 2, 2000

Date	Event	Description
25 May 2011	Amended	Feedback incorporated.
25 May 2011	Review declared as stable	The review is out of date and is being replaced with three protocols evaluating the effect of steroids in growth in children.
25 May 2011	Feedback has been incorporated	Feedback has been added to the review. The review has not been amended in light of the feedback since it is no longer being updated. The unabridged version of the feedback has been sent to the authors of the new protocols.
21 July 2008	Amended	Converted to new review format.
3 March 1999	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

PS: Protocol initiation and development, assessed search results, data extraction, entry and analysis, interpretation and write-up

DB: Protocol initiation and development, assessed search results, data extraction, entry and analysis, interpretation and write-up

FD: Editorial support and guidance throughout

DECLARATIONS OF INTEREST

Neither of the two authors has any affiliations that might place us in a conflict of interest situation. Neither of the two authors has been involved in an included or excluded trial as Principal Investigator, Steering or Monitoring Committee member, Co-Investigator or Site Coordinator. Francine Ducharme MD editor, has received some travel support for meeting attendance, research grant and consulting fees from Glaxo-Dminth Kline Inc.

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Age Factors; Anti-Asthmatic Agents [pharmacology] [*therapeutic use]; Asthma [*drug therapy]; Beclomethasone [pharmacology] [*therapeutic use]; Child Development [drug effects]; Growth [*drug effects]

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MeSH check words

Child; Humans