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Dose Response of Inhaled Corticosteroids in Children With Persistent Asthma: A Systematic Review

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KEY WORDS

inhaled corticosteroids, asthma, dose-response relationship, treatment efficacy, adverse event, systematic review, meta-analysis

ABBREVIATIONS

ICS—inhaled corticosteroid
BDP—beclomethasone dipropionate
RCT—randomized controlled trial
PEF—peak expiratory flow
FEV_1—forced expiratory volume in 1 second
CI—confidence interval
SMD—standardized mean difference
WMD—weighted mean difference
MDI—metered-dose inhaler
DPI—dry powder inhaler

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abstract

OBJECTIVE: To assess the dose-response relationship (benefits and harms) of inhaled corticosteroids (ICSs) in children with persistent asthma.

METHODS: We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) that compared ≥2 doses of ICSs in children aged 3 to 18 years with persistent asthma. Medline was searched for articles published between 1950 and August 2009. Main outcomes of our analyses included morning and evening peak expiratory flow, forced expiratory volume in 1 second, asthma symptom score, β_2-agonist use, withdrawal because of lack of efficacy, and adverse events. Meta-analyses were performed to compare moderate (300–400 μg/day) with low (≤200 μg/day beclomethasone-equivalent) doses of ICSs.

RESULTS: Fourteen RCTs (5768 asthmatic children) that evaluated 5 ICSs were included. The pooled standardized mean difference from 6 trials revealed a small but statistically significant increase of moderate over low doses in improving forced expiratory volume in 1 second (standardized mean difference: 0.11 [95% confidence interval: 0.01–0.21]) among children with mild-to-moderate asthma. There was no significant difference between 2 doses in terms of other efficacy outcomes. Local adverse events were uncommon, and there was no evidence of dose-response relationship at low-to-moderate doses.

CONCLUSIONS: Compared with low doses, moderate doses of ICSs may not provide clinically relevant therapeutic advantage in children with mild-to-moderate persistent asthma. Additional RCTs are needed to clarify the dose-response relationship of ICSs in persistent childhood asthma. *Pediatrics* 2011;127:129–138

Inhaled corticosteroids (ICSs) are currently considered the first-line treatment for persistent childhood asthma; however, uncertainty remains regarding the optimal dose. The most recent asthma guidelines recommend a dose of up to 400 μg/day beclomethasone dipropionate (BDP)-hydrofluoroalkane equivalent for children with mild-to-moderate persistent asthma,[1–3] but these recommendations are generally based on results from individual randomized trials rather than a body of evidence that has been critically appraised by a systematic review.

For adolescent and adult patients, several meta-analyses have revealed that most of the clinical and functional benefits of ICSs are achieved with a dose of ~200 μg/day of fluticasone or equivalent, and the maximum effect is obtained with a dose of ~500 μg/day of fluticasone or equivalent.[4–6] The dose above that leads to minimal further improvement and may be more likely associated with adverse effects.

In childhood asthma, the dose-response relationship of ICSs has not been well established. Several Cochrane systematic reviews in which this issue was addressed included pediatric patients; however, no conclusion has been drawn exclusively for this population.[7–9] Only 1 recently published meta-analysis, which included 7 randomized trials, examined the dose-response relationship of inhaled fluticasone in children with asthma.[10] This study found that the dose-response curve for therapeutic effects of inhaled fluticasone seems to plateau at between 100 and 200 μg/day. However, given that only 2 to 3 trials have contributed available data to the analyses and comparison of only 2 doses (100 vs 200 μg/day), the results of this meta-analysis should be interpreted with caution. Moreover, the adverse effects of inhaled fluticasone were not systematically evaluated in this review. Thus, we conducted a systematic review and meta-analysis to assess the relationship between dose and treatment response (benefits and harms) of ICSs in children with persistent asthma.

METHODS

Data Sources and Search Strategy

We searched the Ovid Medline database for articles published between 1950 and August 2009. The search terms "asthma" and "inhaled corticosteroids" and specific ICSs (beclomethasone, budesonide, fluticasone, mometasone, ciclesonide, triamcinolone, and flunisolide) and their synonyms or brand names were crossed with a highly sensitive search strategy to identify relevant randomized controlled trials (RCTs). Full search strategies are listed in Supplemental Table 4. We also searched the clinical study register of GlaxoSmithKline, the manufacturer of fluticasone and beclomethasone, for potentially relevant unpublished studies. Beside RCTs, we also identified systematic reviews in which ICSs were compared with placebo or different doses of corticosteroids and included children with asthma by searching the Cochrane Database of Systematic Reviews (*The Cochrane Library*, 2009, issue 2) and the Database of Abstracts of Reviews of Effects. Reference lists of identified trials and systematic reviews were scanned for additional relevant trials.

Study Selection

Inclusion and exclusion criteria were defined a priori. To be included in this review, studies had to meet all of the following criteria: (1) study design: RCT; (2) participants: children aged 3 to 18 years at study entry with a diagnosis of persistent asthma based on clinical and/or functional criteria; (3) interventions and comparisons: ICSs given in 2 or more different doses via the same delivery system for at least 4 weeks compared or not with placebo or other interventions; and (4) outcomes: at least 1 of the following measures was obtained: efficacy outcome measures included peak expiratory flow (morning and evening [PEF_{AM} and PEF_{PM}, respectively]), forced expiratory volume in 1 second (FEV_1), asthma symptom score, frequency of nocturnal awakening, frequency of β_2-agonist use, withdrawals because of lack of efficacy, exercise-induced bronchoconstriction expressed as percentage decrease in FEV_1 from the preexercise value, airway hyperresponsiveness measured by the dose of methacholine that caused a 20% reduction in FEV_1 (PD_{20} methacholine), health-related quality of life questionnaire, and airway inflammatory biomarkers (sputum eosinophils, leukotrienes in exhaled breath condensate, or fractional exhaled nitric oxide); safety outcome measures were linear growth, hypothalamic-pituitary-adrenal function, withdrawal because of adverse events, and local adverse events such as oral candidiasis, dysphonia/hoarseness, cough, and pharyngitis/sore throat.

We excluded crossover trials without a washout period or a washout period of <2 weeks, trials that compared single doses of ICSs with placebo or other interventions, trials that included pediatric patients but had no separate data available for the 3- to 18-year age group, and trials that evaluated a stepwise approach to corticotherapy. We also excluded trials that involved patients with a diagnosis of "mild asthma" and were not explicitly classified as having persistent asthma, and clinical and functional parameters of those patients were suggestive of mild intermittent asthma.

Two investigators independently screened the titles and abstracts of publications identified by the searches. Full articles were retrieved

when they seemed to meet the inclusion criteria or there were insufficient data in the titles and abstracts to make a clear decision for their inclusion. The definitive inclusion of trials was made after reviewing the full-text articles. Any disagreement between 2 reviewers about study inclusion was resolved by consensus.

Data Extraction and Assessment of Risk of Bias in Included Studies

Data from each included study were extracted by 1 reviewer using a standardized form and confirmed by another reviewer. Intention-to-treat data sets were used whenever available. Two reviewers independently assessed the risk of bias in included trials by examining the 6 key domains according to the recommendations of the Cochrane Collaboration[11]: (1) method of random-sequence generation; (2) method of allocation concealment; (3) method of blinding; (4) description of incomplete outcome data; (5) evidence of selective outcome reporting; and (6) evidence of other bias. Any disagreement between 2 reviewers about data extraction and study quality assessment was resolved by consensus.

Data Synthesis

We used narratives to summarize the main results of efficacy, safety, and dose-response relationship of ICSs in childhood asthma. Quantitative syntheses were performed whenever there were available data from the primary studies.

Binary data were synthesized by using risk ratios and 95% confidence intervals (CI) as the effect measures. A correction value of 0.5 was added to all cells of a 2-by-2 table with a 0 event. The standardized mean difference (SMD) and 95% CI were used as the metrics of effect size for PEF_{AM}, PEF_{PM}, and FEV_1, because at least 1 of these outcomes was measured as a percentage of predicated values in 2 trials[12,13] but as absolute values in other trials.[14–17] The SMD converts all outcomes to a common scale, measured in units of SDs rather than original units of measurement. This conversion makes it more difficult to interpret the results. For continuous outcomes measured in the same units across studies, such as symptom score and the need for β_2-agonist use, the weighted mean difference (WMD) and 95% CI were used as the effect measures. A random-effects model (DerSimonian and Laird method) was used for the meta-analyses.

For the purpose of this review, the daily doses of ICSs were converted into a BDP-hydrofluoroalkane equivalent, with a dose ratio of 1/1 for budesonide (1/2 for nebulized budesonide) and BDP via chlorofluorocarbon metered-dose inhaler (MDI) or dry powder inhaler (DPI), and 2/1 for fluticasone, mometasone, ciclesonide, and Qvar (IVAX LLC, Teva Group, Petah, Tikva, Israel) BDP-hydrofluoroalkane. These dose equivalents, recommended in the British asthma guidelines, are based on randomized efficacy trials that compared different ICSs, as well as pharmacokinetic proprieties of the drugs.[3]

We planned a priori 3 pairwise comparisons of different daily doses of ICSs (BDP-equivalent): 100 to 200 vs $>$200 to 400 μg/day; $>$200 to 400 vs $>$400 μg/day; and 100 to 200 vs $>$400 μg/day. However, there were sufficient data only for 1 comparison (300–400 vs $\leq$200 μg/day), which corresponded approximately to comparison of moderate and low doses of ICSs.

We estimated the heterogeneity among studies that used the I^2 statistic. I^2 ranges from 0% to 100% and measures the degree of inconsistency across studies; values of 25%, 50%, and 75% correspond to low, moderate, and high heterogeneity, respectively.[18]

We planned to perform subgroup analyses to explore the possible causes for heterogeneity across studies, such as type of corticosteroids, drug-delivery device, interval of administration, duration of treatment, and severity of asthma. We conducted sensitivity analyses that excluded 2 trials in which PEF_{AM}, PEF_{PM}, and/or FEV_1 were measured as a percentage of the predicated values rather than absolute values.[12,13] Sensitivity analyses were also conducted to compare 3 methods (DerSimonian and Laird, Mantel-Haenszel, and Peto) of meta-analysis for rare events such as the majority of adverse events of ICSs. The Peto and Mantel-Haenszel methods were reported to be less biased for meta-analysis with rare events.[11]

The statistical analysis was performed by using Stata 11.0 (Stata Corp, College Station, TX). Reporting of this review follows the recommendation of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement.[19]

RESULTS

From 1687 citations identified through the electronic search, 37 full-text articles were retrieved for further evaluation. Twenty-four articles were excluded: 4 had a treatment period of $<$4 weeks,[20–23] 5 included patients with a diagnosis of probable mild intermittent asthma,[24–28] 5 included patients younger than 3 years,[29–33] 3 evaluated a stepwise approach to corticotherapy,[34–36] 3 were crossover or consecutive treatment studies without a washout period or a washout period of $<$2 weeks,[37–39] and 4 were nonrandomized studies or subgroup reporting of a previous study.[40–43] Thirteen randomized trials were included in the review (Fig 1).[12–17,44–50] One additional relevant study was found by searching the reference lists of 16 systematic reviews.[51] This unpublished

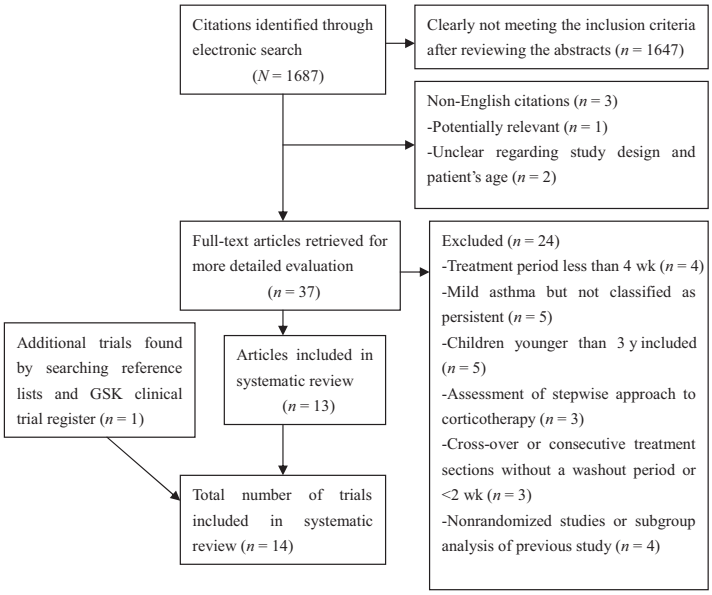

FIGURE 1
Flow diagram of trial identification and selection.

trial was also located by searching the GlaxoSmithKline clinical trial register. From this database, we also obtained some relevant unreported data for 3 included trials.[13,14,16]

Table 1 summarizes the characteristics of 14 included trials. All were multicenter, randomized, double-blind, and parallel-group trials that involved a total of 5768 children with persistent asthma who were living in 26 countries across 5 continents (Africa, Asia, Europe, North America, and South America). All trials were sponsored by multinational pharmaceutical companies that manufacture ICSs. Despite the fact that all trials were described as randomized and double-blind, the methods of random-sequence generation and allocation concealment were explicitly reported for only 5[13,17,46,49,50] and 1 trials,[17] respectively. For this reason, the risk of bias was classified as unclear for the majority of the included trials.

Dose-Response Relationship for Efficacy

For all 8 placebo-controlled efficacy trials, significant benefits of ICSs in improving clinical and functional outcome measurements were reported, despite the variation in type of corticosteroids, daily dose, drug-delivery device, interval of administration, duration of treatment, and severity of asthma.[12–14,16,44,45,47,48] The lowest effective daily doses of ICSs used in the primary studies were 40, 80, 100, 100, and 200 μg/day for ciclesonide (hydrofluoroalkane MDI), beclomethasone (hydrofluoroalkane Autohaler), fluticasone (Diskhaler), mometasone (DPI), and budesonide (Turbuhaler), respectively.

Table 2 shows the pooled results of the comparisons of clinical and functional benefits between moderate and low doses of ICSs. Six trials in children with mild-to-moderate persistent asthma contributed data to the meta-analyses.[12–17] The results were presented as the mean change from baseline to the end point, defined as the last measurement,[13,14,16] or to completion of the trial.[12,15,17] All pooled effect estimates (SMD) were in favor of moderate doses in improving PEF_{AM}, PEF_{PM}, FEV_1, asthma symptom score, and the need for β_2-agonist use, but the difference was statistically significant only for FEV_1 (pooled SMD: 0.11 [95% CI: 0.01–0.21]). No significant heterogeneity across studies was observed in any outcomes ($I^2 = 0\%$) except the need for β_2-agonist use ($I^2 = 65\%$). In sensitivity analyses, a statistically significant superiority of moderate over low doses of ICSs was also observed only for FEV_1 (pooled WMD: 0.028 L [95% CI: 0.002–0.06]). The small number of included trials made it impossible to perform planned subgroup analyses.

There was no significant difference between moderate and low doses of ICSs in terms of withdrawal because of lack of efficacy (Fig 2).

Dose-Response Relationship for Adverse Events

Three trials assessed adverse effects of ICSs given at different doses on linear growth. From 2 trials, there was no report of any significant effects of 1-year treatments with fluticasone (100 and 200 μg/day) or ciclesonide (40 and 160 μg/day) compared with placebo.[14,17] The pooled result from 2 trials revealed no significant difference between effects of moderate and low doses of ICSs on linear growth velocity (WMD: −0.13 cm/year [95% CI −0.29 to 0.03]). Authors of the other trial reported that all 1-year active treatments with beclomethasone (BDP 800 μg/day, BDP 400 μg/day, and BDP 400 μg/day plus salmeterol 100 μg/day) resulted in a decrease in linear growth velocity, and a greater growth reduction was observed with high doses of BDP (800 μg/day).[49]

Eight trials assessed the effects of ICSs on hypothalamic-pituitary-adrenal function, but the reported data were not suitable for meta-analysis. Five 12-week and one 52-week placebo-controlled trials did not reveal significant effects of ICSs on adrenal function, irrespective of type and dose of ICS.[13,16,17,45,47,48] For 2 no-placebo–controlled trials, some

TABLE 1 Characteristics of 14 Multicenter, Randomized, Double-Blind, and Parallel-Group Trials

Study (Year), Country, Sponsor	Duration, wk	Age, y	Male, %	Inclusion Criteria	Intervention and Comparison	Outcomes
Allen et al[15] (1998); United States; GlaxoSmithKline	52	4–11	75	Mild-to-moderate asthma-ATS criteria; 46% received ICSs before entry; entry criteria for FEV_1: ≥60% predicted	FLU Diskhaler 100 μg/d BID (n = 111); FLU Diskhaler 200 μg/d BID (n = 108); placebo (n = 106)	Linear growth rate (cm/y), adverse events
Katz et al[14] (1998); France, Finland, Israel, Italy, Hong Kong, Portugal, Spain, Singapore, United Arab Emirates; GlaxoSmithKline	12	4–11	63.1	Mild asthma; no treatment with ICSs 3 mo before entry; mean baseline PEF: 82% predicted	FLU DPI 100 μg/d BID (n = 85); FLU DPI 200 μg/d BID (n = 86); placebo (n = 92)	FEV_1, PEF, asthma symptom score, β_2-agonist use, nighttime awakenings, adverse events
Peden et al[16] (1998); United States; GlaxoSmithKline	12	4–11	62.6	Moderate asthma-ATS criteria; all required maintenance treatment before entry; entry criteria for FEV_1: 50%–85% predicted	FLU Diskus 100 μg/d BID (n = 90); FLU Diskus 200 μg/d BID (n = 87); FLU Diskhaler 100 μg/d BID (n = 91); FLU Diskhaler 200 μg/d BID (n = 83)	FEV_1, PEF, asthma symptom score, β_2-agonist use, nighttime awakenings, adverse events, morning plasma cortisol levels, 24-h urine cortisol/creatinine concentrations
Shapiro et al[47] (1998); United States; Astra USA, Inc	12	4–8	61.8	Moderate-to-severe asthma-NIH criteria; all required ICSs before entry; entry criteria for FEV_1: ≥50% predicted	BUD nebulizer 0.5 mg/d BID (n = 47); BUD nebulizer 1.0 mg/d BID (n = 42); BUD nebulizer 2.0 mg/d BID (n = 45); placebo (n = 44)	FEV_1, PEF, asthma symptom score, β_2-agonist use, adverse events, basal and adrenocorticotrophic hormone–stimulated plasma cortisol levels
Shapiro et al[48] (1998); United States; Astra USA, Inc	12	6–18	77.7	Moderate-to-severe asthma; all required ICSs before entry; entry criteria for FEV_1: ≥50% to ≤85% predicted	BUD Turbuhaler 200 μg/d BID (n = 102); BUD Turbuhaler 400 μg/d BID (n = 100); BUD Turbuhaler 800 μg/d BID (n = 99); placebo (n = 103)	FEV_1, PEF, asthma symptom score, β_2-agonist use, adverse events, basal and adrenocorticotrophic hormone–stimulated plasma cortisol levels
Verberne et al[49] (1998); Netherlands; GlaxoSmithKline	54	6–16	58.0	Mild-to-moderate asthma-ATS criteria; all received ICSs before enrollment; entry criteria for FEV_1: 55%–90% predicted	BDP Diskhaler 400 μg/d BID (n = 57); BDP Diskhaler 800 μg/d BID (n = 60); BDP 400 μg/d + SAL 100 μg/d BID (n = 60)	FEV_1, PEF, asthma symptom score, β_2-agonist use, airway hyperresponsiveness, adverse events
Shapiro et al[12] (2001); United States; Astra USA, Inc	12	6–17	64.9	Mild-to-moderate asthma-ATS criteria; all received ICSs before entry; entry criteria for FEV_1: ≥65% to ≤90% predicted	BUD Turbuhaler 200 μg/d QD (n = 90); BUD Turbuhaler 400 μg/d QD (n = 93); placebo (n = 91)	FEV_1, PEF, asthma symptom score, β_2-agonist use, adverse events
Nayak et al[13] (2002); United States; 3M Pharmaceuticals	12	5–12	63.5	Moderate asthma; entry criteria for FEV_1: 50%–80% predicted	BDP HFA Autohaler 80 μg/d BID (n = 120); BDP HFA Autohaler 160 μg/d BID (n = 117); placebo (n = 116)	FEV_1, PEF, asthma symptom score, β_2-agonist use, adverse events, morning plasma cortisol levels
Verona et al[50] (2003); Bulgaria, Croatia, Hungary, Poland, Russia; GlaxoSmithKline	52	4–14	72.0	History of asthma requiring high-dose ICSs for ≥4 wk before entry; mean baseline PEF: 255–257 L/min	FLU Diskus 200 μg/d BID (n = 267); FLU Diskus 400 μg/d BID (n = 261)	PEF, asthma symptom score, β_2-agonist use, adverse events, 12-h urine cortisol/creatinine levels
Berger et al[44] (2006); United States; Schering-Plough Corp	12	4–11	62.9	Mild-to-moderate asthma; all received ICSs before entry; entry criteria for FEV_1: ≥60% to ≤85% predicted	MOM DPI 100 μg/d QD (n = 98); MOM DPI 200 μg/d QD (n = 99); placebo (n = 99)	FEV_1, PEF, FVC, $FEF_{25\%-75\%}$, asthma symptom score, HRQoLQ, adverse events
Gelfand et al[45] (2006); United States, Mexico, Poland; Aventis Pharmaceuticals	12	4–11	—	Moderate-to-severe asthma, NIH criteria (59.4% moderate, 24.1% severe); entry criteria for FEV_1: ≥40% to ≤90% predicted	CIC HFA MDI 40 μg/d QD (n = 252); CIC HFA MDI 80 μg/d QD (n = 259); CIC HFA MDI 160 μg/d QD (n = 253); placebo (n = 254)	FEV_1, PEF, asthma symptom score, β_2-agonist use, HRQoLQ, adverse events, 24-h urine cortisol/creatinine levels

TABLE 1 Continued

Study (Year), Country, Sponsor	Duration, wk	Age, y	Male, %	Inclusion Criteria	Intervention and Comparison	Outcomes
Skoner et al[17] (2008); Argentina, Chile, United States, Venezuela; Sanofiaventis, Altana, Nycomed	52	5–8.5	67.2	Mild asthma, NIH criteria; no treatment with ICSs 30 d before entry; entry criteria for FEV_1: ≥80% predicted	CIC HFA MDI 40 μg/d QD ($n = 221$); CIC HFA MDI 160 μg/d QD ($n = 219$); placebo ($n = 221$)	Linear growth rate (cm/y), adverse events, 24-h urine cortisol/creatinine concentrations
Pedersen et al[46] (2009); Brazil, Germany, Hungary, Poland, Portugal, South Africa; Nycomed	12	6–11	65.4	Moderate-to-severe asthma-ATS criteria (32.3% moderate, 54.8% severe); 49.2% used ICSs before entry; entry criteria for FEV_1: 50%–90% predicted	CIC HFA MDI 80 μg/d QD ($n = 252$); CIC HFA MDI 160 μg/d QD ($n = 242$); FLU HFA MDI 176 μg/d BID ($n = 250$)	FEV_1, PEF, asthma symptom score, β_2-agonist use, airway hyperresponsiveness, HRQoLQ, adverse events, 24-h urine cortisol/creatinine concentrations
FLIP39[51]; Belgium, Eire, Finland, Israel, Italy, Netherlands, United Kingdom; GlaxoSmithKline	12	6–16	—	Moderate-to-severe asthma; all received ICSs for before entry; entry criteria for PEF: ≤95% predicted	FLU DPI 100 μg/d BID ($n = 97$); FLU DPI 200 μg/d BID ($n = 99$)	FEV_1, PEF, asthma symptom score, β_2-agonist use, nighttime awakenings, adverse events.

ATS indicates American Thoracic Society; FLU, fluticasone; BID, twice daily; NIH, National Institutes of Health; BUD, budesonide; SAL, salmeterol; MOM, mometasone; QD, once daily; HRQoLQ, health-related quality-of-life questionnaire; CIC, ciclesonide; HFA, hydrofluoroalkane; —, data not available.

TABLE 2 Comparison of Moderate and Low Doses of ICSs in Terms of Clinical and Functional Benefits

Study	ICS	Moderate vs Low Doses, μg/d	Improvements from baseline									
			PEF_{AM}, L/min or % Predicted[a]		PEF_{PM}, L/min or % Predicted[a]		FEV_1, L or % Predicted[b]		Symptom Score		β_2-Agonist Use, Puffs per d	
			Mean, SE	SMD (95% CI)	Mean (SE)	SMD (95% CI)	Mean (SE)	SMD (95% CI)	Mean (SE)	WMD (95% CI)	Mean (SE)	WMD (95% CI)
Allen et al[15] (1998)	FLU Diskhaler	200 vs 100	—	—	—	—	0.25 (0.03)vs 0.20 (0.02)	0.20 (−007 to 0.47)	—	—	—	—
Katz et al[14] (1998)	FLU DPI	200 vs 100	57 (3.9) vs 50 (5.0)	0.17 (−0.13 to 0.47)	53 (3.9) vs 44 (4.0)	0.24 (−0.06 to 0.54)	0.25 (0.03) vs 0.17 (0.03)	0.29 (−0.02 to 0.59)	−0.44 (0.06) vs −0.43 (0.08)	−0.01 (−0.21 to 0.19)	−1.14 (0.19) vs −0.73 (0.16)	−0.41 (−0.91 to 0.09)
Peden et al[16] (1998)	FLU Diskus	200 vs 100	40 (5.0) vs 34 (3.0)	0.16 (−0.14 to 0.45)	34 (4.0) vs 26 (3.0)	0.24 (−0.05 to 0.54)	0.24 (0.03) vs 0.22 (0.03)	0.08 (−0.24 to 0.39)	−0.41 (0.07) vs −0.36 (0.07)	−0.05 (−0.24 to 0.14)	−1.04 (0.19) vs 0.08 (0.23)	−1.12 (−1.71 to −0.52)
Peden et al[16] (1998)	FLU Diskhaler	200 vs 100	42 (4.0) vs 41 (5.0)	0.02 (−0.28 to 0.32)	36 (4.0) vs 36 (4.0)	0.0 (−0.29 to 0.29)	0.23 (0.04) vs 0.24 (0.03)	−0.03 (−0.35 to 0.29)	−0.36 (0.07) vs −0.41 (0.07)	0.05 (−0.14 to 0.25)	−0.90 (0.23) vs −1.02 (0.18)	0.12 (−0.45 to 0.69)
Shapiro et al[12] (2001)	BUD Turbuhaler	400 vs 200	1.3 (1.3) vs 2.9 (1.3)	−0.13 (−0.42 to 0.16)	2.4 (1.3) vs 1.8 (1.2)	0.05 (−0.24 to 0.34)	2.7 (1.6) vs 2.3 (1.6)	0.03 (−0.26 to 0.32)	—	—	—	—
Nayak et al[13] (2002)	BDP HFA Autohaler	160 vs 80	—	—	—	—	10.1 (1.2) vs 9.1 (1.1)	0.08 (−0.18 to 0.33)	—	—	−0.58 (0.12) vs −0.26 (0.18)	−0.32 (−0.74 to 0.10)
Skoner et al[17] (2008)	CIC HFA MDI	160 vs 40	—	—	—	—	0.15 (0.01) vs 0.13 (0.01)	0.11 (−0.08 to 0.29)	—	—	—	—
Pooled result	—	—	0.05 (−0.09 to 0.20)		0.13 (−0.02 to 0.28)		0.11 (0.01 to 0.21)		−0.003 (−0.12 to 0.11)		−0.42 (−0.87 to 0.03)	

FLU indicates fluticasone; BUD, budesonide; HFA, hydrofluoroalkane; CIC, ciclesonide; —, not available/applicable.

[a] PEF_{AM} and PEF_{PM} were measured as percent predicted by Shapiro et al[12] and L/min by Katz et al[14] and Peden et al.[16]

[b] FEV_1 was measured as percent predicted by Nayak et al[13] and Shapiro et al[12] and liters by Allen et al,[15] Katz et al,[14] Peden et al,[16] and Skoner et al.[17]

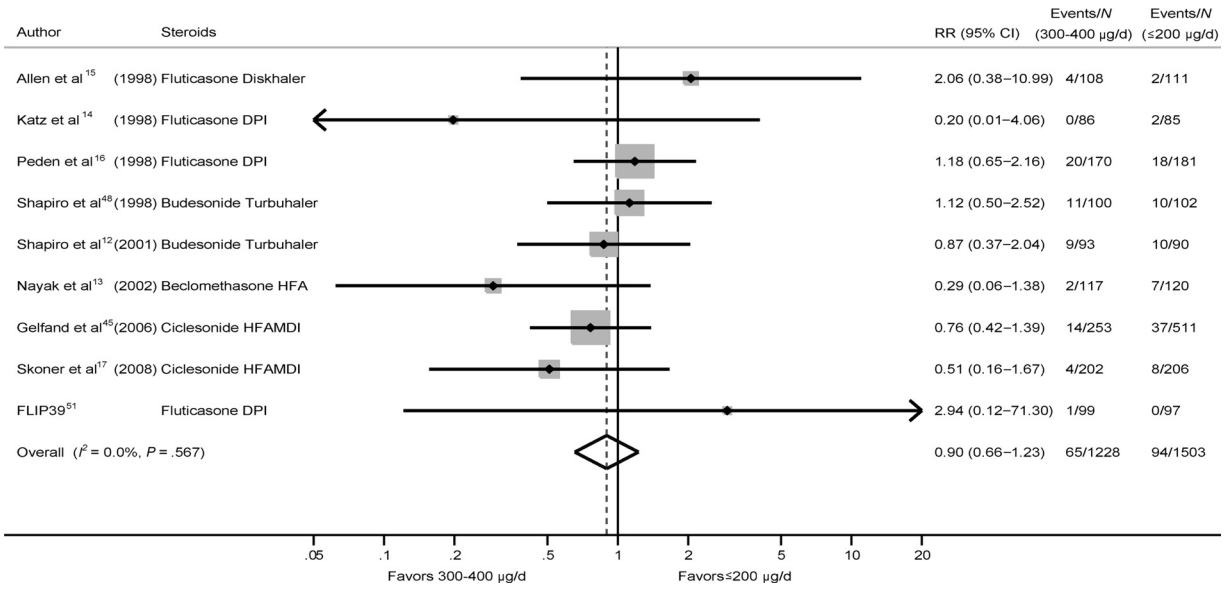

FIGURE 2

Comparison of moderate (300–400 μg/day) and low (≤200 μg/day) doses of ICSs in terms of withdrawal as a result of lack of efficacy. HFA indicates hydrofluoroalkane; RR, risk ratio.

biochemical evidence of adrenal suppression related to ICSs was reported. One showed a small but statistically significant lower 12-hour urine cortisol/creatinine level after 52 weeks of treatment with fluticasone 400 μg/day compared with fluticasone 200 μg/day.[50] Another trial found that a 12-week treatment with fluticasone 176 μg/day, but not ciclesonide 80 or 160 μg/day, resulted in a significant decrease from the baseline in 24-hour urine cortisol/creatinine concentrations.[46]

Table 3 summarizes the pooled results of the comparisons of local adverse events and withdrawal because of adverse effects between moderate and low doses of corticosteroids. Oral candidiasis and dysphonia/hoarseness were uncommon (overall rate: <1% in patients treated with ICSs). The most common adverse event was pharyngitis/sore throat (overall rate: 7.7%). There was no significant difference between moderate and low doses of ICSs in terms of local adverse events and withdrawal as a result of adverse effects. No significant heterogeneity across studies was observed in any outcomes (I^2 = 0%) except dysphonia/hoarseness (I^2 = 39%). Sensitivity analyses using 3 different methods (DerSimonian and Laird, Mantel-Haenszel, and Peto) yielded similar results. Subgroup analyses were not performed because of the small number of included trials.

DISCUSSION

Methodologic Limitations

Some methodologic limitations should be taken into account when interpreting the results of this review. First, all trials were described as randomized and double-blind, but the risk of bias was unclear in the majority of studies, because the methods of random-sequence generation and allocation concealment were not explicitly reported. Second, nonuniform reporting of continuous efficacy outcome results and incomplete data collection and reporting of adverse events led to a small number of trials contributing available data for meta-analyses of the dose response of efficacy and safety of ICSs. This limitation not only reduced the power of this review to show a significant dose-response relationship but may have also produced biased results. Third, because of language limitation we did not include 1 randomized trial conducted in Germany that involved 24 children with mild-to-moderate persistent asthma.[52] This 8-week trial compared 2 doses (200 vs 800 μg/day) of budesonide. Given the small number of patients and the use of airway inflammation markers as efficacy outcomes, exclusion of this study from the review would not lead to significant changes of the results of the meta-analyses.

Evidence for Dose-Response Relationship of Efficacy

Meta-analysis of the data was only available for comparison of moderate and low doses of ICSs and the small number of trials contributed to the analyses. The pooled SMD suggests the superiority of moderate over low doses of ICSs in improving FEV_1 among children with mild-to-moderate persistent asthma. However, the increase of FEV_1 was small (28 mL) and probably only of marginal clinical relevance. There was no evidence of dose-response relationship of ICSs for other clinical and functional outcomes.

No significant difference was found between moderate and low doses of ICSs in

TABLE 3 Comparison of Moderate and Low Doses ofICSs in Terms of Local Adverse Events and Withdrawal Because of Adverse Effects

Study	ICS	Moderate vs Low Doses, μg/d	Adverse Events, No. of Events/No. of Patients; RR (95% CI)				
			Withdrawals	Oral Candidiasis	Dysphonia/ Hoarseness	Cough	Pharyngitis/Sore Throat
Allen et al[15] (1998)	FLU Diskhaler	200 vs 100	1/108 vs 0/111; 3.08 (0.13, 74.85)	1/108 vs 3/111; 0.34 (0.04–3.24)	0/108 vs 3/111; 0.15 (0.01–2.81)	4/108 vs 3/111; 1.37 (0.31–5.98)	1/108 vs 4/111; 0.26 (0.03–2.26)
Katz et al[14] (1998)	FLU DPI	200 vs 100	4/87 vs 5/85; 0.79 (0.22–2.84)	2/87 vs 1/85; 1.95 (0.18–21.15)	3/87 vs 0/85; 6.84 (0.36–130.47)	0/87 vs 1/85; 0.32 (0.01–7.89)	—
Shapiro et al[48] (1998b)	BUD Turbuhaler	400 vs 200	—	1/100 vs 0/102; 3.06 (0.13–74.22)	—	—	—
Peden et al[16] (1998)	FLU DPI	200 vs 100	1/170 vs 3/170; 0.40 (0.15–1.11)	—	—	—	—
Shapiro et al[12] (2001)	BUD Turbuhaler	400 vs 200	4/93 vs 5/90; 0.77 (0.21–2.79)	—	—	—	6/93 vs 4/90; 1.45 (0.42–4.97)
Nayak et al[13] (2002)	BDP HFA Autohaler	160 vs 80	1/117 vs 1/120; 1.03 (0.06–16.21)	—	—	9/117 vs 7/120; 1.32 (0.51–3.42)	9/117 vs 13/120; 0.71 (0.32–1.60)
Berger et al[44] (2006)	MOM DPI	200 vs 100	—	0/99 vs 0/98	—	—	5/99 vs 9/98; 0.55 (0.19–1.58)
Gelfand et al[45] (2006)	CIC HFA MDI	160 vs 40–80	16/253 vs 41/515; 0.79 (0.45–1.39)	2/253 vs 1/515; 4.07 (0.37–44.69)	—	—	14/253 vs 22/515; 1.14 (0.70–1.86)
Skoner et al[17] (2008)	CIC HFA MDI	160 vs 40	8/219 vs 14/221; 0.58 (0.25–1.35)	0/219 vs 0/221	0/219 vs 0/221	—	37/219 vs 44/221; 0.85 (0.57–1.26)
Pedersen et al[46] (2009)	CIC HFA MDI	160 vs 80	—	1/242 vs 0/252; 3.12 (0.13–76.30)	—	—	—
FLIP39[51]	FLU DPI	200 vs 100	2/99 vs 6/97; 0.33 (0.07–1.58)	—	1/99 vs 1/97; 0.98 (0.06–15.40)	3/99 vs 1/97; 2.94 (0.31–27.77)	1/99 vs 3/97; 0.33 (0.04–3.09)
Pooled result	—	—	—	7/1108 vs 5/1384; 1.65 (0.52–5.25)	4/513 vs 4/514; 0.99 (0.12–8.33)	16/411 vs 12/413; 1.35 (0.65–2.81)	73/988 vs 99/1252; 0.88 (0.67–1.45)

RR indicates risk ratio; FLU, fluticasone; BUD, budesonide; HFA, hydrofluoroalkane; MOM, mometasone; CIC, ciclesonide; —, not available/applicable.

terms of withdrawal because of lack of efficacy. Despite the fact that most of the study reports did not clearly describe the criteria for "lack of efficacy," this outcome is generally defined by using clinical and/or functional parameters indicating no improvement or even worsening.[14,15] These results suggest that moderate doses of ICSs do not provide additional therapeutic benefits over low doses of ICSs in children with mild-to-moderate persistent asthma.

Evidence for Dose-Response Relationship of Adverse Events

Although ICSs are generally considered safe treatment for children with asthma, the potential systemic adverse effects such as adrenal suppression, linear growth retardation, and effects on bone mass, are still of concern.[53] A limited number of studies included in this review assessed adverse effects of ICSs given at different doses on linear growth and on hypothalamic-pituitary-adrenal function, and their findings were inconsistent. There are no suitable data for investigating dose-response relationship of systemic adverse effects of ICSs.

Local adverse events of ICSs, such as oropharyngeal candidiasis, dysphonia (hoarseness), sore throat, and cough, have no serious consequences but may lead to poor tolerability and adherence with treatment.[54]These adverse effects generally result from the deposition of active drugs in the oropharynx during inhalation. The incidence of local adverse events of ICSs vary widely across studies, probably because of variation in type and dose of ICSs, drug-delivery device, and study methodology.[54] In this review, the most common local adverse event was pharyngitis/sore throat (overall rate: 7.7%). Oral candidiasis and dysphonia/ hoarseness were uncommon (overall rate: $<$1%). There was no evidence of dose-response relationship of ICSs at low-to-moderate doses in terms of local adverse events and withdrawal because of adverse events.

CONCLUSIONS

Current evidence is insufficient to define the dose-response relationship of ICSs in terms of efficacy and safety in children with persistent asthma. However, at least 2 observations could be made on the basis of the data of this review: (1) Compared with low doses ($\leq$200 μg/day), moderate doses (300−400 μg/day) of ICSs may not provide clinically relevant therapeutic advantage for children with mild-to-moderate persistent asthma, and the likelihood of withdrawal because of lack of efficacy seems to be similar at 2 dose ranges. (2) There is no evidence of a dose-response relationship of ICSs at low-to-moderate doses in terms of local adverse events and withdrawal because of adverse events.

The results of this review reveal a significant gap in understanding the

dose-response relationship of ICSs in children with persistent asthma, which makes it impossible to recommend the optimal doses of ICSs for these patients. Additional high-quality randomized trials are needed to compare efficacy and safety of different doses of ICSs in children with persistent asthma, especially higher dose ranges in patients with more severe asthma. Differences in responsiveness to ICSs may be expected between severe and mild or moderate persistent asthma and between ICS-naive patients and those receiving ICSs at study entry.[55] Previous trials have generally not taken these factors into account in study design. The small number of trials included in this review also makes it impossible to address this issue. Future trials should use stratified randomization to ensure comparability between dose groups in terms of asthma severity and baseline ICS use. The trials should be large enough for performing subgroup analyses to assess whether dose-response effects of ICSs vary significantly among patients with different characteristics. FEV_1 and PEF were used as the primary efficacy outcomes in most previous trials; however, the magnitude of changes necessary to be considered clinically relevant has not been well defined for the pediatric population. The composite efficacy outcome consisting of clinical and functional parameters, such as the level of asthma control recommended by the Global Initiative for Asthma,[1] may be considered an appropriate efficacy end point in future trials. Trial reporting should follow the CONSORT (Consolidated Standards of Reporting Trials) recommendations to facilitate future synthesis of evidence on dose-response relationship of ICSs in childhood asthma.[56] Data collection and reporting of adverse events of ICSs should be improved.

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Dose Response of Inhaled Corticosteroids in Children With Persistent Asthma: A Systematic Review

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ERRATA

Claure N, et al. Multicenter Crossover Study of Automated Control of Inspired Oxygen in Ventilated Preterm Infants. *Pediatrics*. 2011;127(1):e76–e83

An error occurred in the article by Claure et al (doi: 10.1542/peds.2010-0939). The second sentence of the Figure 1 legend reads:

> The hourly median FiO_2 values during the 24 hours of the automated period (open triangles) remained consistently lower than the hourly median FiO_2 values during the 24-hour manual period (closed triangles).

The Figure 1 legend should read:

> The hourly median FiO_2 values during the 24 hours of the automated period (closed triangles) remained consistently lower than the hourly median FiO_2 values during the 24-hour manual period (open triangles).

doi:10.1542/peds.2011-0133

L Zhang, et al. Dose Response of Inhaled Corticosteroids in Children With Persistent Asthma: A Systematic Review. *Pediatrics*. 2011;127(1):129–138

An error occurred in this article by Zhang et al (doi: 10.1542/peds.2010-1223). The Financial Disclosure currently reads, "The authors have indicated they have no financial relationships relevant to this article to disclose." This should have read, "This study was supported by a Brazilian National Council for Scientific and Technological Development (CNPq) research grant (67/2009-REBRATS)."

doi:10.1542/peds.2011-0216

P Hovi, et al. Intima-media thickness and flow-mediated dilatation in the Helsinki Study of Very Low Birth Weight Adults. *Pediatrics*. 2011;127(2):e304–e311

A data management error occurred in this article by Hovi et al (doi: 10.1542/peds.2010-2199) that resulted in a change in the number of current smokers. The authors have rerun all corresponding analyses and ascertained that the mistake left the other results unaffected.

On page number e307, under "Endothelial Vasodilatory Function," it reads, "After adjusting for BMI or with only the 136 nonsmokers included, the difference in FMD remained similar." This should have read: "After adjusting for BMI or with only the 127 nonsmokers included, the difference in FMD remained similar."

In Supplemental Table 2, "Characteristics of Participants With or Without Ultrasound Measurements," under "Current smoker," (regarding the VLBW subjects) the row reads from left to right, "16 (22.5); 14 (15.2); .23; 1.00". This should have read: "20 (28.2); 15 (16.3); .07; .12."

In the same table, under "Current smoker," (regarding the term born subjects) the row reads, "17 (16.8); 10 (14.7); .71". This should have read: "39 (38.6); 18 (26.5); .10."

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