Effectiveness of prophylactic inhaled steroids in childhood asthma: A systematic review of the literature

Caroline Calpin, MD, Colin Macarthur, MBChB, PhD, Derek Stephens, MSc, William Feldman, MD, and Patricia C. Parkin, MD *Toronto, Ontario, Canada*

Background: There has been no systematic appraisal of the evidence regarding the effectiveness of prophylactic inhaled steroids in childhood asthma.
Objective: We sought to evaluate the effectiveness of prophylactic inhaled steroids in childhood asthma.
Methods: A MEDLINE search from January 1966 through December 1996 was used to identify pertinent English-language publications. All randomized, double-blind, placebo-controlled trials of prophylactic inhaled steroid therapy for childhood asthma that included data on clinical outcomes (symptom scores and concomitant drug use) or laboratory outcomes (peak expiratory flow rate) were included.
Results: In total, 24 of 93 studies retrieved met the inclusion criteria. The overall weighted relative improvement in mean total symptom score (inhaled steroid vs placebo) was 50% (95% confidence interval [CI]: 49%, 51%), the overall weighted relative decrease in mean concomitant β_2-agonist use (inhaled steroid vs placebo) was 37% (95% CI: 36%, 38%), and the overall weighted relative decrease in mean concomitant oral steroid use (inhaled steroid vs placebo) was 68% (95% CI: 66%, 70%). The overall weighted absolute improvement in mean peak expiratory flow rate (inhaled steroid vs placebo) was 38 L/min (95% CI: 34.3 L/min, 41.7 L/min).
Conclusions: Prophylactic inhaled steroids are effective, compared with placebo, in improving both clinical and laboratory outcomes in childhood asthma. (J Allergy Clin Immunol 1997;100:452-7.)

Key words; Asthma, drug therapy, glucocorticoid, inhaled corticosteroid, inhaled steroid, clinical trial, randomized controlled trial

Asthma is the most common chronic disease of childhood, with an estimated prevalence ranging from 5% to 30% in some developed countries.[1, 2] The pharmacologic treatment of childhood asthma has evolved considerably over the last 2 decades, and the prophylactic use of inhaled steroids is now more common.[3] Although inhaled steroids have been advocated as first-line prophylaxis for moderate to severe childhood asthma,[4] recent studies in adults suggest that patients with milder asthma may also benefit.[5-7] Furthermore, it has been suggested that long-term inhaled steroid treatment may induce remission.[8, 9]

Abbreviations used
CI: Confidence interval
PEFR: Peak expiratory flow rate
RIM: Relative improvement in mean

The inflammatory basis of asthma is well established,[10, 11] and there is conclusive evidence that inhaled steroids decrease airway inflammation and bronchial hyperresponsiveness.[12, 13] Several long-term studies have also shown the clinical efficacy of inhaled steroids in the treatment of childhood asthma in terms of reduction of symptoms.[14-16] These earlier studies were open trials, meaning that no comparison group was used. Subsequently, there have been numerous controlled, double-blind studies that have assessed various aspects of inhaled steroid prophylaxis. Despite the abundance of literature, however, there has been no systematic appraisal of the evidence quantifying the effectiveness of prophylactic inhaled steroids in the treatment of childhood asthma. The objective of this review was to synthesize the results of all published, randomized, double-blind, placebo-controlled trials of inhaled steroid prophylaxis in children with asthma.

METHODS

A computer search of the MEDLINE Bibliographic Data Base (January 1966 through December 1996) was used to identify pertinent articles. Medical subject headings included asthma, drug therapy, glucocorticoid, inhaled corticosteroid, inhaled steroid, clinical trial, and randomized controlled trial. In addition, *Current Contents* and selected pediatric and respiratory journals were searched manually. Only English–language publications were retrieved. Cited references from these articles and from reviews on childhood asthma were also collected. The search was restricted to the "best quality" evidence (i.e., only randomized, double-blind, placebo-controlled trials of prophylactic inhaled steroid therapy in children with asthma 0 to 18 years of age) were included.

Data on the effectiveness of prophylactic inhaled steroid therapy on clinical outcomes (symptom scores, occurrence of cough or wheeze, frequency of concomitant oral steroid or β_2-agonist use) and laboratory outcomes (peak expiratory flow rate [PEFR]) were gathered. Outcome data from each article were independently abstracted by three physicians, with consensus agreement used for ambiguously reported data.

From the Pediatric Outcomes Research Team (PORT), Division of General Pediatrics, The Hospital for Sick Children and the Department of Pediatrics, University of Toronto, Toronto.
Received for publication June 14, 1996; revised May 15, 1997; accepted for publication May 20, 1997.
Reprint requests: Patricia Parkin, MD, FRCPC, Division of General Pediatrics, The Hospital for Sick Children, 555 University Ave., Toronto, Ontario, Canada M5G 1X8.

0091-6749/97 $5.00 + 0 **1/1/83340**

For most of the studies retrieved, symptom scores were recorded by parents using daily diary cards. A variety of individual symptoms were assessed (e.g., wheeze, cough, breathlessness, tightness of chest, rhinitis, degree of happiness, and activity intolerance). In all studies a higher symptom score reflected worse symptoms. Mean total symptom scores for the two groups (inhaled steroid and placebo) were often reported; however, the subjective measurement of clinical symptoms was not consistent across trials. For example, different studies used different measurement scales, with data rarely provided on the reliability or validity of the instruments. Also, fewer than one fifth of the studies provided information on the variability around mean scores (e.g., standard deviations or standard errors). Because these data were commonly missing, calculation of a confidence interval (CI) around the difference in scores for the two groups was often difficult. Several studies also reported mean cough and wheeze scores for the two groups. If both daytime and nighttime scores were provided, we used the nighttime cough score and the daytime wheeze score in the calculation of treatment effect.

Measurement of concomitant drug use also varied across trials. For example, several studies used total drug dose over the study period as the primary outcome; whereas other studies reported total number of doses, number of days of concomitant use, number of patients requiring use, or number of asthmatic episodes requiring concomitant use.

Given the limitations of and variability in the reported outcome data, a formal meta-analysis was not considered appropriate. However, in an effort to standardize the treatment effect across studies, for the clinical outcomes (symptom scores and concomitant drug use) the relative improvement in mean (RIM) clinical outcome was calculated as follows[17]:

$$\text{RIM} = \frac{(\text{Mean clinical outcome [placebo group]} - \text{Mean clinical outcome [steroid group]}) \times 100}{\text{Mean clinical outcome (placebo group)}}$$

For example, in the study by Frears et al,[18] at 8 weeks' follow-up, the mean symptom score in the placebo group was 64 and in the inhaled steroid group, 18.8 (a higher score denotes worse symptomatology). Therefore a 71% RIM symptom score was noted for the inhaled steroid group compared with the placebo group ([64.0 − 18.8] ÷ 64.0).

To provide summary estimates of clinical effect (inhaled steroid vs placebo), overall mean RIM for each clinical outcome was calculated. These summary estimates were weighted by taking into account individual study sample size.[19] The standard error of each weighted RIM was calculated by using the Jackknife estimate,[20] with a 95% CI derived from this estimate of standard error. Finally, the sign test was used to determine the probability of the observed distribution of positive studies for each clinical outcome (i.e., those demonstrating a relative improvement in clinical outcome for the steroid group compared with the placebo group).[21]

The laboratory outcome, PEFR, was measured in a consistent and standardized manner across the different trials, either as liters per minute or percent predicted. Therefore the absolute improvement in mean PEFR, the difference in mean PEFR between the steroid group and the placebo group, was calculated for each study. An overall weighted mean absolute improvement in mean PEFR was calculated,[19] with estimation of a 95% CI around the point estimate by using the Jackknife estimate of the standard error.[20] The sign test was also applied to these results.

The influence of potential modifiers such as steroid dose (>400 μg vs ≤400 μg), duration of inhaled steroid (>4 weeks vs ≤4 weeks), patient age (>5 years vs ≤5 years), and asthma severity (oral steroid–dependent vs non-oral steroid–dependent) was assessed by comparing treatment effect sizes in these subgroups. Differences in weighted mean summary scores between the subgroups were tested by using the nonparametric Mann-Whitney U test.[21] All reported side effects were documented along with hospitalization rates and emergency department visits.

RESULTS

In total, the MEDLINE search identified 93 studies, of which 24 were randomized, double-blind, placebo-controlled trials of inhaled steroid use in childhood asthma.[18, 22-44] A list of the excluded studies is available from the author on request. Most of the excluded studies were neither double-blind, randomized, nor controlled ($n = 48$). Other reasons for exclusion included a control treatment other than placebo (e.g., sodium cromoglycate, theophylline, or combination therapy; $n = 7$), nonprophylactic use of inhaled steroid ($n = 4$), or failure to report on any of the outcome measures previously specified ($n = 6$). The features of the included studies are described in Table I. In total, 1087 children were studied in the 24 clinical trials, with study sample sizes ranging from 18 to 258 children. Thirteen (57%) of the trials involved school-aged children, whereas 10 (42%) involved preschool-aged children (age was not specified in one study). Five of the trials (22%) involved children with oral steroid–dependent asthma only. Several different inhaled steroids were used as the experimental treatment, with variation also in the dose and route of delivery. The median duration of steroid use was 8 weeks (range, 4 to 88 weeks). The effectiveness of treatment (inhaled steroid vs placebo) for the clinical and laboratory outcomes is shown in Table II.

Symptom scores

Outcome data on total symptom scores were reported in 15 studies. Thirteen of the 15 studies reported an improvement in total symptom score in the inhaled steroid group compared with the placebo group (sign test, $p < 0.01$). The overall weighted RIM total symptom score (inhaled steroid vs placebo) was equal to 50% (95% CI: 49%, 51%).

Cough and wheeze

Cough scores were provided in 11 trials. Nine of the 11 studies showed an improvement in the inhaled steroid group compared with placebo (sign test, $p < 0.05$), with an overall weighted RIM cough score (inhaled steroid vs placebo) of 24% (95% CI: 23%, 25%). Sixteen studies reported wheeze scores, with 15 of the 16 studies demonstrating an improvement in the inhaled steroid group (sign test, $p < 0.01$), with an overall weighted RIM wheeze score (inhaled steroid vs placebo) equal to 36% (95% CI: 35%, 37%).

TABLE I. Characteristics of the randomized placebo-controlled trials of prophylactic inhaled steroids in childhood asthma

Reference	Study design	*n*	Age (yr)		Treatment		Duration of therapy (wk)
			Range	Mean	Inhaled steroid	Daily dose + route	
Frears[18]	Crossover	22	4-15	9	Betamethasone valerate	NA MDI	4
Howard[22]	Crossover	22*	7-16	NA	Betamethasone valerate	800 μg MDI	4
Taylor[23]	Crossover	18	7-15	11	Betamethasone valerate	800 μg MDI	8
Lovera[24]	Crossover	21	6-20	11	Beclomethasone dipropionate	400 μg MDI	6
Klein[25]	Crossover	22	N/A	11	Beclomethasone dipropionate	400 μg MDI	4
Richards[26]	Parallel	27*	6-14	10	Beclomethasone dipropionate	NA MDI	12
Hiller[27]	Parallel	26	6-14	9	Beclomethasone dipropionate	300 μg MDI	4
Shapiro[28]	Parallel	32*	5-16	10	Flunisolide	1 mg MDI	12
Meltzer[29]	Parallel	48	6-15	10	Flunisolide	1 mg MDI	6
Orgel[30]	Parallel	34*	5-15	9	Flunisolide	1 mg MDI	14
Webb[31]	Crossover	20	1-5	3	Beclomethasone dipropionate	150 μg Neb	8
Storr[32]	Parallel	29	1-6	4	Beclomethasone dipropionate	300 μg Neb	24
Katz[33]	Parallel	44	6-12	9	Beclomethasone dipropionate	400 μg MDI	8
Gleeson[34]	Crossover	39	2-6	4	Budesonide	400 μg Nbh	6
Carlsen[35]	Parallel	44	0-2	1	Beclomethasone dipropionate	200-400 μg Neb	8
van Bever[36]	Crossover	23	0-2	1	Budesonide	1 mg Neb	4
Bisgaard[37]	Parallel	77	0-3	2	Budesonide	800 μg Nbh	12
Piacentini[38]	Parallel	20	8-13	10	Flunisolide	1 mg Neb	8
van Essen-Zandvliet[39]	Parallel	116	7-16	11	Budesonide	600 μg MDI	88
Noble[40]	Crossover	29	0-2	1	Budesonide	300 μg Nbh	6
Ilangovan[41]	Parallel	36*	0-5	2	Budesonide	2 mg Neb	8
Mackenzie[42]	Parallel	258	6-14	9	Fluticasone propionate	100 μg DI	4
Connett[43]	Parallel	40	1-3	2	Budesonide	400-800 μg MDI	24
de Blic[44]	Parallel	40	0-3	2	Budesonide	2 mg Neb	12

NA, Not available; *MDI,* metered dose inhaler; *Neb,* nebulizer; *Nbh,* nebuhaler; *DI,* disk inhaler.
*Oral steroid-dependent asthmatic children.

Concomitant drug use

Fourteen studies assessed concomitant β–agonist use, with 13 of 14 reporting decreased use in the inhaled steroid group compared with the placebo group (sign test, $p < 0.01$); and an overall weighted relative decrease in mean β–agonist use (inhaled steroid vs placebo) was 37% (95% CI: 36%, 38%). A different group of 12 studies reported on concomitant oral steroid use, with 10 of 12 showing decreased use in the inhaled steroid group (sign test, $p < 0.05$). The overall weighted relative decrease in mean concomitant oral steroid use (inhaled steroid vs placebo) was equal to 68% (95% CI: 66%, 70%).

PEFR

Thirteen trials used PEFR as a primary outcome measure. (One trial estimated PEFR both in liters per minute and as percent predicted.) All nine studies that reported PEFR in liters per minute noted an improvement in the inhaled steroid group compared with the placebo group (sign test, $p < 0.01$), with an overall weighted absolute improvement in mean PEFR (inhaled steroid vs placebo) equal to 38 L/min (95% CI: 34.3 L/min, 41.7 L/min). Similarly, all five trials that reported PEFR as percent predicted showed improvement in the inhaled steroid group compared with the placebo group (sign test, $p < 0.01$), with an overall weighted absolute improvement in mean PEFR (inhaled steroid vs placebo) equal to 11% predicted value (95% CI: 9.5% predicted, 12.5% predicted).

Modifiers

In general, inhaled steroids appeared to be more effective (compared with placebo) in reducing symptoms in older children (>5 years vs ≤5 years), in children with severe disease (oral steroid–dependent vs nondependent), and at higher doses (>400 μg vs ≤400 μg). These differences, however, were not statistically significant.

Hospitalizations

In four of five studies[26, 31, 39, 42] in which hospital admissions were assessed, there were no hospitalizations in the inhaled steroid group compared with a range of two to six hospitalizations per study period in the placebo group. In the fifth study,[43] the inhaled steroid group had eight hospitalizations during the study period, and the placebo group had three. These differences in admission rates, however, did not reach statistical significance in any study.

Side effects

All studies but one reported side effects. Six studies commented that no side effects were found but did not elaborate. All adverse effects reported were minor and

TABLE II. Effectiveness of treatment, prophylactic inhaled steroid versus placebo, in children with asthma

Reference	Symptoms			Medication Use		PEFR	
	Total symptoms RIM (%)	Cough RIM (%)	Wheeze RIM (%)	β-agonist RIM (%)	Oral steroid RIM (%)	L/min AIM	Predicted AIM (%)
Frears[18]	71*			59	100	46*	
Howard[22]	87*				85*		8*
Taylor[23]	73*	14*	22*	65*		77*	
Lovera[24]			75	59	100		
Klein[25]	72*					57*	
Richards[26]			65*		86		19
Hiller[27]	8			40			29*
Shapiro[28]		33*	9		41*	182	
Meltzer[29]	20*	24	29*			20	
Orgel[30]		24*	12		−23	29*	
Webb[31]	0	−23	−32	34	0		
Storr[32]		29	21*	47*			
Katz[33]		50*	16				
Gleeson[34]		27	41				12*
Carlsen[35]	38*		18*	65*			
Van Beaver[36]	−14	0	23	−14			
Bisgaard[37]			80*		100		
Piacentini[38]	88*					21	
Van Essen-Zandvliet[39]	33*			12	69*	33*	
Noble[40]	70	35	53*	27			
Ilangovan[41]	80*			57	25*		
Mackenzie[42]	32			11		19*	9*
Connett[43]		45*	27	57*	50		
de Blic[44]	89*		81*	41	100*		
Weighted mean	50	24	36	37	68	38	11
(95% (CI)	(49, 51)	(23, 25)	(35, 37)	(36, 38)	(66, 70)	(34.3, 41.7)	(9.5, 12.5)

AIM, Absolute improvement in mean PEFR.
*$p < 0.05$.

were not severe enough in any study to warrant stopping randomized treatment. In all 12 studies that assessed adrenal function, no evidence of corticosteroid-induced adrenal suppression was found. Similarly, in all eight studies that specifically mentioned monitoring of height velocity, there were no differences between the placebo and inhaled steroid groups in terms of growth. In five of the 11 studies that monitored *Candida* throat cultures, no growth in either group was demonstrated. In three studies the inhaled steroid group had more positive *Candida* throat cultures; in two studies the groups were similar; and in one study the placebo group had more positive *Candida* cultures. In the seven studies that reported on candidiasis, four studies showed clinical cases (one patient with thrush in each inhaled steroid group); however, all cases responded promptly to treatment and the candidiasis did not interfere with feeding. Finally, all four studies in which periodic eye examinations were performed showed no evidence of cataract formation in the study subjects.

DISCUSSION

This systematic review of the published literature demonstrates the effectiveness of prophylactic inhaled steroids in childhood asthma. A marked improvement in all clinical and laboratory parameters in the inhaled steroid group compared with the placebo group was noted in the majority of studies. Although the overall weighted absolute improvement in mean peak expiratory flow of 38 L/min is of questionable clinical significance, the overall weighted absolute improvement in mean percent predicted PEFR of 11% for the inhaled steroid group has greater clinical usefulness and meaning.[45] A strength of this review was that only the best quality evidence (i.e., from randomized, double-blind, placebo-controlled trials) was used. However, although the literature review was comprehensive, several limitations existed, and it is possible that some eligible studies (both published and unpublished) were not retrieved. The only data base searched was the MEDLINE Bibliographic Data Base, and only English-language publications were cited, thereby excluding publications in more obscure journals and non-English–language publications. Despite these restrictions, studies from around the globe were retrieved: 46% of the references cited were British, 29% were North American, and 25% were European (of which half were Scandinavian).

It is well documented that negative clinical trials are less likely to be submitted for publication and less likely to be published. The phenomenon of publication bias is, however, more evident in observational and laboratory-based studies than in experimental studies such as the

publications included in our study.[46] Furthermore, three negative studies were captured by this review.[30, 31, 36] Although in theory it is possible to calculate the fail-safe number of negative studies that would be required to overturn the reported benefits of inhaled steroid therapy,[47] the lack of data that precluded our ability to do a formal meta-analysis also made it impossible to perform this calculation (i.e., standard normal deviates and exact *p* values were not provided for the majority of studies). Given the strength of the findings, however, it is unlikely that inclusion of such studies (if any) would materially alter the conclusions of this review.

The reviewed studies were not homogeneous because trials differed by source population, patient age, and asthma severity, as well as by type, dose, and duration of inhaled steroid. Despite these differences, the superior results in the inhaled steroid group were consistent, suggesting that the findings may be generalizable. Synthesis of the results from a heterogeneous group of studies may obscure differences in effectiveness of inhaled steroids in specific populations. Although the effectiveness of inhaled steroids in reducing symptoms of asthma appeared to be greater in those studies in which larger doses were used, in older children, and in those patients with severe disease, these differences were not statistically significant. However, the small number of studies in each subgroup resulted in low statistical power to detect differences.

Other important clinical outcomes such as hospital admission or emergency department visits were studied in only five trials. The trend in these studies suggested that prophylactic inhaled steroid use reduced use of these health care resources. This finding may be important, given the recent data showing increasing hospital admission rates because of childhood asthma,[48, 49] along with evidence that suggests that inhaled steroid prophylaxis may decrease readmission in childhood asthma.[50] Despite the extensive body of literature establishing the effectiveness of inhaled steroids in childhood asthma, their use in clinical practice may be less frequent than is optimal. For example, a survey of children with asthma attending an urban pediatric tertiary hospital emergency department reported that fewer than half of the children deemed eligible for prophylactic asthma medications (including inhaled steroids) were actually receiving medication.[51] The most likely reason for physician reluctance to prescribe inhaled steroids for children is concern about side effects.

Potential systemic side effects include suppression of the hypothalamic–pituitary–adrenal axis, effects on bone metabolism, and interference with growth.[3] The evidence from numerous studies in children, however, suggests that inhaled steroids have minimal side effects at doses of up to 400 μg/day. For example, in the absence of previous or concomitant use of oral steroid preparations, inhaled steroid use in children has little effect on pituitary–adrenal function.[38, 52] Likewise, studies of bone metabolism in growing children receiving oral and inhaled steroids have shown little if any effect.[53, 54] Long-term studies of up to 5 years have demonstrated that inhaled steroids have no significant effects on statural growth in children.[39, 55, 56] A recent meta-analysis of 21 studies involving over 800 children concluded that moderate-dose beclomethasone dipropionate therapy (as used in the majority of studies in this review) did not have a clinically significant effect on linear growth.[57]

Although studying the safety of inhaled steroid treatment was not the primary objective of the studies included in this review, no significant side effects were reported in any of the 23 studies in which they were monitored. All adverse effects reported were minor and not sufficient to stop treatment. Specifically, there were no documented deleterious effects of inhaled steroid therapy in terms of growth, adrenal function, or cataract formation. In all the studies, only four cases of oral candidiasis were documented.

In conclusion, prophylactic inhaled steroids are effective in improving both clinical parameters and peak flow rates in children with asthma. Clinical effectiveness was demonstrated in children with both moderate and severe (i.e., oral steroid–dependent) asthma and across a wide age range after a median duration of therapy of around 8 weeks. Other studies have shown that the risk of significant systemic side effects associated with inhaled steroid therapy in children appears to be extremely low. Because insufficient use of steroid prophylaxis may be associated with poorly controlled asthma and subsequent morbidity and cost, the challenge is to incorporate the evidence on the effectiveness and safety of inhaled steroid prophylaxis in childhood asthma into clinical practice.

REFERENCES

1. Strachan D, Butland B, Anderson H. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. Br Med J 1996;312:1195-9.
2. Pearce N, Weiland S, Keil U, Langridge P, Anderson HR, Strachan D, et al. Self reported prevalence of asthma symptoms in children in Australia, England, Germany and New Zealand: an international comparison using the Isaac protocol. Eur Respir J 1993;6:1455-61.
3. Barnes P. Inhaled glucocorticoid for asthma. N Engl J Med 1995; 332:868-75.
4. Warner J. Asthma—a follow-up statement from an international paediatric asthma consensus group. Arch Dis Child 1992;67:240-8.
5. Lorentzson S, Boe J, Ericksson G, Persson G. Use of inhaled corticosteroids in patients with mild asthma. Thorax 1990;45:733-5.
6. Reed C. Aerosol steroids as primary treatment of mild asthma. N Engl J Med 1991;325:425-6.
7. Haahtela T, Jarvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. N Engl J Med 1994;331:700-5.
8. van Essen-Zandvliet E, Hughes M, Waalkens H, Duiverman E, Kerrebijn K. Remission of childhood asthma after long-term treatment with inhaled corticosteroid (budesonide): Can it be achieved? Eur Respir J 1994;7:63-8.
9. Juniper E, Kline P, Vanzieleghem M, Ramsdale E, O'Byrne P, Hargreave F. Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in non-steroid-dependent asthmatics. Am Rev Respir Dis 1990;142:832-6.
10. Pedersen S, Hansen OR. Budesonide treatment of moderate and

severe asthma in children: a dose-response study. J Allergy Clin Immunol 1995;95:29-33.
11. Barnes P. Mechanisms of asthma. Medicine International 1991;89: 3694-702.
12. Bennati D, Piacentini G, Peroni D, Sette L, Testi R, Boner A. Changes in bronchial reactivity in asthmatic children after treatment with beclomethasone alone or in association with salbutamol. J Asthma 1989;26:359-64.
13. Kerrebijn K, van Essen-Zandvliet E, Neijens H. Effect of long-term treatment with inhaled corticosteroids and beta-agonists on the bronchial responsiveness in children with asthma. J Allergy Clin Immunol 1987;79:653-9.
14. Godfrey S, Balfour-Lynn L, Tooley M. A three to five year follow up of the use of aerosol steroid beclomethasone diproprionate in childhood asthma. J Allergy Clin Immunol 1978;62:335-59.
15. Godfrey S, Konig P. Treatment of childhood asthma for 13 months and longer with beclomethasone dipropionate. Clin Allergy 1974;4: 325-30.
16. Brown H, Bhowmik M, Jackson F, Ng T. Beclomethasone dipropionate aerosols in the treatment of asthma in childhood. Practitioner 1976;31:309-14.
17. Guyatt G, Sackett D, Cook D. Users' guide to the medical literature II. How to use an article about therapy or prevention. JAMA 1994;271:59-63.
18. Frears J, Wilson L, Friedman M. Betamethasone 17-valerate by aerosol in childhood asthma. Arch Dis Child 1973;48:856-63.
19. Fleiss JL. The design and analysis of clinical experiments. New York: John Wiley; 1986. p. 149-54.
20. Effron B, Tibshirani R. The Jackknife. An introduction to the bootstrap. New York: Chapman Hall; 1993. p. 141-52.
21. Kramer M. Clinical epidemiology and biostatistics: a primer for clinical investigators and decision-makers. 1st ed. New York: Springer-Verlag; 1988. p. 159-62.
22. Howard K, Jacoby N. Betamethasone valerate treatment of steroid dependent children. Postgrad Med J 1974;50(suppl 4):41-4.
23. Taylor B, Norman A. Betamethasone valerate aerosol in children not on previous steroid therapy. Postgrad Med J 1974;50(suppl 4):44-9.
24. Lovera J, Collins-Williams C, Bailey J. Beclomethasone dipropionate by aerosol in the treatment of asthmatic children. Postgrad Med J 1975;51(suppl 4):94-8.
25. Klein R, Waldman D, Kershnar H. Treatment of chronic childhood asthma with beclomethasone dipropionate aerosol. I. A double-blind crossover trial in nonsteroid-dependent patients. Pediatrics 1977;60: 7-13.
26. Richards W, Platzker A, Church JA, Yamamoto F, Foster S. Steroid-dependent asthma treated with inhaled beclomethasone dipropionate in children. Ann Allergy 1978;41:274-7.
27. Hiller E, Groggin R, Lenney W, Stokes M, Milner A. Beclomethasone dipropionate powder inhalation treatment in chronic childhood asthma. Prog Respir Res 1981;17:285-9.
28. Shapiro G, Izu A, Furukawa C, Pierson W, Bierman C. Short-term double-blind evaluation of flunisolide aerosol for steroid-dependent asthmatic children and adolescents. Chest 1981;80:671-5.
29. Meltzer E, Kemp J, Orgel A, Izu A. Flunisolide aerosol for treatment of severe chronic asthma in steroid-independent children. Pediatrics 1982;69:340-5.
30. Orgel H, Meltzer E, Kemp J. Flunisolide aerosol in the treatment of steroid-dependent asthma in children. Ann Allergy 1983;51:21-5.
31. Webb M, Milner A, Hiller E, Henry R. Nebulised beclomethasone dipropionate suspension. Arch Dis Child 1986;61:1108-10.
32. Storr J, Lenney C, Lenney W. Nebulised beclomethasone dipropionate in pre-school asthma. Arch Dis Child 1986;61:270-3.
33. Katz R, Rachelefsky G, Siegel S, Spector S, Rohr A. Twice-daily beclomethasone dipropionate in the treatment of childhood asthma. J Asthma 1986;23:1-7.
34. Gleeson J, Price J. Controlled trial of budesonide given by the nebuhaler in pre-school children with asthma. Br Med J 1988;298: 163-6.
35. Carlsen K, Leegaard J, Larsen S, Orstavik J. Nebulised beclomethasone dipropionate in recurrent obstructive episodes after acute bronchiolitis. Arch Dis Child 1988;63:1428-33.
36. van Bever H, Schuddinck L, Wojciechowski M, Stevens W. Aerosolized budesonide in asthmatic infants: a double bind study. Pediatr Pulmonol 1990;9:177-80.
37. Bisgaard H, Nunck S, Nielsen J, Petersen W, Ohlsson S. Inhaled budesonide for treatment of recurrent wheezing in early childhood. Lancet 1990;336:649-51.
38. Piacentini G, Sette L, Peroni D, Bonizzato C, Bonetti S, Boner A. Double-blind evaluation of effectiveness and safety of flunisolide aerosol for treatment of bronchial asthma in children. Allergy 1990;45:612-6.
39. van Essen-Zandvliet E, Hughes MD, Waalkens HJ, Duiverman EJ, Pocock SJ, Kerrebijn KF. Effects of 22 months of treatment with inhaled corticosteroids and/or beta-2-agonists on lung function, airway responsiveness, and symptoms in children with asthma. Am Rev Respir Dis 1992;146:547-54.
40. Noble V, Ruggins N, Everard M, Milner A. Inhaled budesonide for chronic wheezing under 18 months of age. Arch Dis Child 1992;67: 285-8.
41. Ilangovan P, Pedersen S, Godfrey J, Nikander K, Noviski N, Warner J. Treatment of severe steroid dependent pre-school asthma with nebulized budesonide suspension. Arch Dis Child 1993;68:356-9.
42. Mackenzie C, Weinberg E, Tabachnik E, Taylor M, Havnen J, Crescenzi K. A placebo controlled trial of fluticasone propionate in asthmatic children. Eur J Pediatr 1993;152:856-60.
43. Connett GJ, Warde C, Wooler E, Lenney W. Use of budesonide in severe asthmatics aged 1-3 years. Arch Dis Child 1993;69:351-5.
44. de Blic J, Delacourt C, Le Bourgeois M, Mahut B, Ostinelli J, Caswell C, et al. Efficacy of nebulized budesonide in treatment of severe infantile asthma: a double-blind study. 1996;98:14-20.
45. Sly P. Peak expiratory flow monitoring in pediatric asthma. J Asthma 1996;33:277-87.
46. Easterbrook P, Berlin J, Gopalan R, Mathews D. Publication bias in clinical research. Lancet 1991;337:867-72.
47. Rosenthal R. The "file drawer problem" and tolerance for null results. Psychol Bull 1979;86:638-41.
48. Wilkins K, Mae Y. Trends in rates of admission to hospital and death from asthma among children and young adults in Canada during the 1980's. Can Med Assoc J 1993;148:185-90.
49. Taylor W, Newacheck P. Impact of childhood asthma on health. Pediatrics 1992;90:657-62.
50. Macarthur C, Calpin C, Parkin PC, Feldman W. Factors associated with pediatric asthma readmissions. J Allergy Clin Immunol 1996; 98(suppl):992-3.
51. Dougherty G, Spadafora G. The use of prophylactic drugs in pharmacologic management of pediatric asthma [abstract]. Arch Pediatr Adolesc Med 1994;148:66.
52. Phillip M, Aviram M, Lieberman E. Integrated plasma cortisol concentration in children with asthma receiving long-term inhaled corticosteroids. Pediatr Pulmonol 1991;12:84-9.
53. Konig P, Hillman L, Cervantes C. Bone metabolism in children with asthma treated with inhaled beclomethasone diproprionate. J Pediatr 1993;122:219-26.
54. Wolthers O, Riis B, Pederson S. Bone turnover in asthmatic children treated with oral prednisolone or inhaled budesonide. Pediatr Pulmonol 1993;16:341-6.
55. Ninan T, Russell G. Asthma, inhaled corticosteroid treatment, and growth. Arch Dis Child 1992;67:703-5.
56. Volovitz B, Amir J, Malik H, Kauschansky A, Varsano I. Growth and pituitary-adrenal function in children with severe asthma treated with inhaled budesonide. N Engl J Med 1993;329:1703-8.
57. Allen D, Mullen M, Mullen B. A meta-analysis of the effect of oral and inhaled steroids on growth. J Allergy Clin Immunol 1994;93: 967-76.