Published as: *Internet J Pediatr Neonatol*. 2006 ; 6(1): .

Inhaled Corticosteroids Adverse Events In Asthmatic Children: A Review

Saad Alotaibi, FAAP, FRCPC and
Pediatric Respiratory Specialist, Farwanyah Hospital, Kuwait

Farhan Alshammari, KBFM
Family Physician Specialist, Jahra Health Area, Kuwait

Abstract

Background—Inhaled corticosteroids (ICS) have an important role in the treatment of chronic asthma in children. The prevalence of asthma symptoms in children varies from 0 to 30 percent in different populations with the highest prevalence occurring in Australia, New Zealand and England.

Methods—A review of the literature and studies about inhaled corticosteroids safety, action and adverse events in children and adults where applicable was done.

Conclusion—Inhaled corticosteroids are the main stay therapy for persistent asthma in children. Their safety and efficacy is proven from the literature. Proper education of the parents about asthma and inhaled corticosteroids is very important and improve asthma control. Keeping in mind to taper the inhaled corticosteroids to the lowest dose needed to control asthma and using correct inhalation technique by the use of spacers with metered dose inhalers or dry powder inhalers (Turbuhaler and Diskus) will prevent the occurrence of adverse events.

Keywords

Inhaled corticosteroids; adverse events

Background

Inhaled glucocorticosteroids, are currently the most effective long-term preventive medications and are effective in reducing asthma attacks[1, 2]. The anti-inflammatory action of corticosteroids was discovered in 1948. Inhaled corticosteroids (ICS) are highly lipophilic, rapidly enter the airway cells and bind to cytosolic receptors. The Glucocorticoid–Receptor (GR) complexes then moves quickly into the nucleus and bind to the Glucocorticoid responsive elements of genes, which will be either increasing or decreasing gene transcription of cytokine production. They also bind to, and disrupt the activity of other transcription factors in the nucleus. They inhibit transcription of the genes for cytokine production [3]. They have direct inhibitory effects on macrophages, t-lymphocytes, eosinophils, and airway epithelial cells [4,5,6]. Also they reduce the number of mast cells within the airway and inhibit plasma exudation and mucus secretion [7]. It has been found that after treatment with ICS for 1–3 months there is marked reduction in the numbers of mast cells, macrophages, t-lymphocytes, and eosinophils in the bronchial epithelium and submucosa of asthmatics. Inhaled corticosteroids decrease airway hyperresponsiveness to histamine, cholinergic agonists, allergens, exercise, fog, cold air, bradykinin, adenosine, and

Correspondence to: Saad Alotaibi.

irritants such as sulfur dioxide and metabisulfites [8]. Safety and adverse effects of ICS has been a concern for both physicians and patients.

Discussion

It is proven that ICS are effective in controlling asthma symptoms. In a study of children 7 to 17 years old, those using the ICS showed a marked improvement in symptoms, peak-expiratory-flow variability, and lung function as compared with a group receiving regular treatment with b-agonists [9]. In studies of preschool children and infants, glucocorticoids inhaled through a large-volume spacer also improved asthma symptoms and reduced the number of exacerbations [10, 11]. It was also documented that the accelerated annual decline in lung function typical of patients with asthma has been slowed by such treatment. A safe ICS will have a Short receptor binding half-life, Rapid first pass and inactivation in Liver, Low Lipophilicity and short plasma half-life [12]. Comparing the binding affinity to human Glucocorticoid receptors in vitro between different ICS it was found that Flunisolide has the lowest relative receptor affinity, Triamcinolone is twice that of Flunisolide, Budisonide is twice that of Triamcinolone, Beclomethasone (active metabolite) twice that of budesonide and Fluticasone twice that of beclomethasone [13]. It has been described that beclomethasone and fluticasone are the highest lipophilic ICS, 1000 and 2500 times more than Flunisolide [14].

After inhalation a large proportion of the inhaled dose, 80 to 90 percent, is deposited on the oropharynx and swallowed. It is then available for absorption into the systemic circulation through the liver. This fraction is markedly reduced if the glucocorticoid is administered through a large-volume spacer attached to a metered-dose inhaler. Rinsing the mouth after the use of a dry-powder inhaler (e.g. Turbuhaler, Diskus) will achieve the same effect. Between 10 and 20 percent of the inhaled drug enters the respiratory tract, where it is deposited in the airways and is available for absorption into the systemic circulation [15]. Most of the studies on the distribution of inhaled glucocorticoids have been conducted in normal subjects and factors such as airway inflammatory disease, airway obstruction, the age of the patient, and concomitant therapy may all alter the disposition of the inhaled dose.

There also may be important differences in the metabolism of different glucocorticoids. Beclomethasone dipropionate, for example, is metabolized to the more active form beclomethasone monopropionate in many types of tissues including lung tissue [16], but there is no information about the formation, absorption, or metabolism of this metabolite in humans. Flunisolide and budesonide are subject to extensive first-pass metabolism in the liver so that less of these drugs reach the systemic circulation [17, 18]. In the other hand fluticasone propionate has a low oral bioavailability[19]. In a meta-analysis of 22 studies showed fluticasone to exhibit significantly steeper dose-related adrenal suppression twice as compared to beclomethasone, 2.5 more than budesonide and 3.6 times more than Triamcinoloneacetonide [20]. Adverse events of inhaled corticosteroids are rarely occurring and there is concern that inhaled corticosteroids might cause adrenal suppression, reduce bone density, short stature, cataract and behaviour changes.

The most common local side effect of ICS is dysphonia, reported in 5 % to 50 % of patients [21]. Oropharyngeal Candidiasis is more common in elderly patients. To reduce these side effects, strategies are aimed at decreasing oropharyngeal deposition of the drug by improving inhalation technique, using a spacer device or Turbuhaler, decreasing the frequency of administration and rinsing the mouth with water.

Suppression of hypothalamic-pituitary-adrenocortical axis has a concern with inhaled corticosteroid therapy. There is no evidence that even high doses of ICS reduce a patient's

plasma cortisol response to the stress produced by an exacerbation of asthma or by insulin-induced hypoglycaemia [22]. In a study by Brown et al when a spacer was used, a daily dose of 2000 μg of beclomethasone or budesonide has no effect on 24-hour urinary cortisol excretion [23]. When metered dose inhaler alone without spacer was used, cortisol level reduced but within normal range [24]. It was found that when Beclomethasone given to children in doses of 800 μg or less it left urinary cortisol excretion unchanged [25]. In studies in which plasma cortisol was measured at frequent intervals, there was a small but significant reduction in nocturnal values when beclomethasone and budesonide were inhaled in doses as low as 400 μg per day [26]. There was no clinical significance with this reduction. Overall, in the absence of previous or concomitant treatment with oral glucocorticoids, inhaled corticosteroids in doses of 400 μg per day or less in children, have little if any effect on pituitary–adrenal function.

For bone metabolism effect it was found that given in a large-volume spacer, even in doses of 2000 μg per day, neither beclomethasone nor budesonide had any effect on plasma osteocalcin concentrations in one study [23]. The urinary excretion of pyridinium cross-links, a sensitive measure of bone and collagen degradation is not increased by inhaled beclomethasone, in a dose of more than 1000 μg per day. Beclomethasone and budesonide, at doses up to 800 μg per day, have no effect on bone metabolism [23, 27]. There is now reassuring evidence that doses of < or = 400 ug for children (1000ug in adult) are safe with no clinically significant adverse effect on bone density or bone growth.

Long-term Longitudinal studies of inhaled corticosteroids effect on growth have demonstrated no significant effect on statural growth of inhaled corticosteroids in doses of up to 800 μg per day for up to five years of treatment [28]. In a longitudinal 3–5 years study of children aged 2–7 years old, inhaled budesonide (200 μg per day) had no effect on growth [29]. This was supported by the findings of a meta-analysis of 21 studies, included 810 children, which showed no effect of inhaled beclomethasone on height, even in children treated with higher doses for a long period [30]. All short and intermediate duration studies, which found that longitudinal statural growth was retarded in children treated with beclomethasone dipropionate 400ug/day, used a fixed dose with no tailoring of this dose in children with mild asthma and the duration of the study was for 1 year only. Also spacers were not used which would improve the therapeutic index of the medication [31]. In a 14 year. Prospective, cohort study of 142 asthmatic children treated with budesonide at a dose of 412ug/day for 9.4 years compared to a control group of asthmatic children who never had inhaled corticosteroids and 51 healthy siblings. All children treated with inhaled corticosteroids attained their adult height to the same extent of the control group [32].

For ocular side effects, in a cross-sectional study of children taking inhaled beclomethasone or budesonide, no cataracts were found on slit-lamp examination, even in patients who had taken 2000 μg per day for more than 10 years [33].

Corticosteroids may cause non-specific central nervous system adverse effects such as emotional lability, anxiety, euphoria, depression, aggressiveness, and insomnia. For inhaled corticosteroids the evidence is limited to isolated case reports in a total of eight patients, two adults and six children [34,35,36,37]. The manifestations have been hyperactive behaviour, aggressiveness, insomnia, uninhibited behaviour, and impaired concentration. One case involved was an adult using nasal spray of beclomethasone dipropionate [34], and the remainder were using inhaled budesonide (200–1,200 ug/day) in one adult and six children under the age of 5 years. In most cases the changes occurred within the first 2 days, and sometimes the causality was proved by improvement on discontinuation and recurrence on reintroducing the same drug. A few patients tolerated lower doses of the same drug or switching from budesonide to beclomethasone. All returned to normal after discontinuation

of the inhaled corticosteroid. The only case report associated with fluticasone is a 52 years old female asthmatic used inhaled Fluticasone 2mg/day and salmeterol for 2 years presented with Cushing's syndrome with proximal myopathy, osteopenia, hypertension, depressive psychosis, and adrenal suppression. Here symptoms improved after treatment changed to Budesonide 0.8mg/day and montelukast [38].

Conclusions

Inhaled corticosteroids are the first line therapy for asthma in all ages [2]. They are the most effective asthma therapy currently available, and numerous studies have documented their long-term efficacy in asthma control in adults and in children. Of paramount importance is the question of safety as inhaled steroids are likely to be required for a long time. The development of side effects to medication will inversely influence the adherence to such medication. Potential but small risk of side effects is well balanced by efficacy. Spacer devices with MDIs and mouth washing with DPIs after inhalation decrease oral candidiasis. High daily doses may be associated with skin thinning and bruises, and rarely adrenal suppression. Local side effects are hoarseness and oropharyngeal candidiasis. Medium and high doses have produced minor growth delay or suppression average 1 cm in children. Attainment of predicted adult height does not appear to be affected [2].

Acknowledgments

Kuwait medical library staff for the help in retrieving the needed articles for the authors.

References

1. Gina. Based On The Workshop Report: Globalstrategy For Asthma Management And Prevention Updated. Pocket Guide For Asthma Management And Prevention In Pocket Guide For. 2004
2. Cac Report: Canadian Asthma Guidelines. Canadian Asthma Consensus Report, 1999. Supplement To Cmaj. 1999:161.
3. Ai Barnes, Pj. Anti-Inflammatory Actions Of Steroids: Molecular Mechanisms. Trends Pharmacol Sci. 1993; 14:436–441. [PubMed: 7510080]
4. Schleimer, Rp. Effects Of Glucocorticosteroids On Inflammatory Cells Relevant To Their Therapeutic Applications In Asthma. Am Rev Respir Dis. 1990; 141:S59–S69. [PubMed: 2178515]
5. Laitinen, La; Laitinen, A.; Haahtela, T. A Comparative Study Of The Effects Of An Inhaled Corticosteroid, Budesonide, And A Beta 2-Agonist, Terbutaline, On Airway Inflammation In Newly Diagnosed Asthma: A Randomized, Double-Blind, Parallel-Group Controlled Trial. J Allergy Clin Immunol. 1992; 90:32–42. [PubMed: 1629507]
6. Djukanovic R, Wilson Jw, Britten Km, Wilson Sj, Walls Af, Roche Wr, Howarth Ph, Holgate St. Effect Of An Inhaled Corticosteroid On Airway Inflammation And Symptoms In Asthma. Am Rev Respir Dis. 1992; 145:669–674. [PubMed: 1546849]
7. Shimura S, Sasaki T, Ikeda K, Yamauchi K, Sasaki H, Takishima T. Direct Inhibitory Action Of Glucocorticoid On Glycoconjugate Secretion From Airway Submucosal Glands. Am Rev Respir Dis. 1990; 141:1044–1049. [PubMed: 2158256]
8. Barnes, Pj. Effect Of Corticosteroids On Airway Hyperresponsiveness. Am Rev Respir Dis. 1990; 141:S70–S76. [PubMed: 2178516]
9. Van Essen-Zandvliet, Ee; 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. The Dutch Chronic Non-Specific Lung Disease Study Group. Am Rev Respir Dis. 1992; 146:547–554. [PubMed: 1355640]
10. Bisgaard H. Use Of Inhaled Corticosteroids In Pediatric Asthma. Pediatr Pulmonol Suppl. 1997; 15:27–33. [PubMed: 9316099]

11. Bisgaard H, Munck Sl, Nielsen Jp, Petersen W, Ohlsson Sv. Inhaled Budesonide For Treatment Of Recurrent Wheezing In Early Childhood. Lancet. 1990; 336:649–651. [PubMed: 1975851]
12. Kelly, Hw. Establishing A Therapeutic Index For The Inhaled Corticosteroids: Part I. Pharmacokinetic/Pharmacodynamic Comparison Of The Inhaled Corticosteroids. J Allergy Clin Immunol. 1998; 102:S36–S51. [PubMed: 9798722]
13. O'byrne, Pm; Pedersen, S. Measuring Efficacy And Safety Of Different Inhaled Corticosteroid Preparations. J Allergy Clin Immunol. 1998; 102:879–886. [PubMed: 9847425]
14. Pedersen S, O'byrne P. A Comparison Of The Efficacy And Safety Of Inhaled Corticosteroids In Asthma. Allergy. 1997; 52:1–34. [PubMed: 9253465]
15. Barnes, Pj. Drug Therapy: Inhaled Glucocorticoids For Asthma. N Engl J Med. 1995; 332:868–875. [PubMed: 7870143]
16. Wurthwein G, Rohdewald P. Activation Of Beclomethasone Dipropionate By Hydrolysis To Beclomethasone-17-Monopropionate. Biopharm Drug Dispos. 1990; 11:381–394. [PubMed: 2207292]
17. Chaplin, Md; Rooks, W., 2nd; Swenson, Ew; Cooper, Wc; Nerenberg, C.; Chu, Ni. Flunisolide Metabolism And Dynamics Of A Metabolite. Clin Pharmacol Ther. 1980; 27:402–413. [PubMed: 7357797]
18. Ryrfeldt A, Andersson P, Edsbacker S, Tonnesson M, Davies D, Pauwels R. Pharmacokinetics And Metabolism Of Budesonide, A Selective Glucocorticoid. Eur J Respir Dis Suppl. 1982; 122:86–95. [PubMed: 6958498]
19. Fd Holliday, Sm; Sorkin, Em. Inhaled Fluticasone Propionate. A Review Of Its Pharmacodynamic And Pharmacokinetic Properties, And Therapeutic Use In Asthma. Drugs. 1994; 47:318–331. [PubMed: 7512904]
20. Lipworth B, Wilson Am. Dose Response To Inhaled Corticosteroids: Benefits And Risks. Semin Respir Crit Care Med. 1998; 19:625–646.
21. Ck Hanania, Na; Kestens. Adverse Effects Of Inhaled Corticosteroids. Am J Med. 1995; 98:196–208. 61. Am J Med 1995, 98:196–208. [PubMed: 7847437]
22. Bg Brown, Ph; Greening, Ap; Crompton, Gk. High Dose Inhaled Steroid Therapy And The Cortisol Stress Response To Acute Severe Asthma. Respir Med. 1992; 86:495–497. [PubMed: 1470707]
23. Ms Brown, Ph; Shearing, C.; Tibi, L.; Greening, Ap; Crompton, Gk. Systemic Effects Of High Dose Inhaled Steroids: Comparison Of Beclomethasone Dipropionate And Budesonide In Healthy Subjects. Thorax. 1993; 48:967–973. [PubMed: 8256242]
24. Fg Pedersen S. Urine Cortisol Excretion In Children Treated With High Doses Of Inhaled Corticosteroids: A Comparison Of Budesonide And Beclomethasone. Eur Respir J. 1988; 1:433–435. [PubMed: 3169214]
25. Prahl P. Adrenocortical Suppression Following Treatment With Beclomethasone And Budesonide. Clin Exp Allergy. 1991; 21:145–146. [PubMed: 2021872]
26. Bisgaard H, Damkjaer Nielsen M, Andersen B, Andersen P, Foged N, Fuglsang G, Host A, Leth C, Pedersen M, Pelck I, et al. Adrenal Function In Children With Bronchial Asthma Treated With Beclomethasone Dipropionate Or Budesonide. J Allergy Clin Immunol. 1988; 81:1088–1095. [PubMed: 3288682]
27. Hl Konig P, Cervantes Ci, et al. Bone Metabolism In Children With Asthma Treated With Inhaled Beclomethasone Dipropionate. J Pediatr. 1993; 122:219–226. [PubMed: 8429434]
28. Rg Ninan, Tk. Asthma, Inhaled Corticosteroid Treatment, And Growth. Arch Dis Child. 1992; 67:703–705. [PubMed: 1626989]
29. Aj Volovitz B, 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; 329:1703–1708. [PubMed: 8232459]
30. Mm Allen, Db; Mullen, B. A Meta-Analysis Of The Effect Of Oral And Inhaled Corticosteroids On Growth. J Allergy Clin Immunol. 1994; 93:967–976. [PubMed: 8006318]
31. Pederson S. Am J Respir Crit Care Med. 2001; 164:521–535. [PubMed: 11520710]
32. Agertoft P. Effect Of Long Term Treatment With Inhaled Budesonide On Adult Height In Children With Asthma. N Engl J Med. 2000; 343:1064–1069. [PubMed: 11027740]

33. Pm Simons, Fe; Gillespie, Ca; Cheang, M.; Shuckett, Ep. Absence Of Posterior Subcapsular Cataracts In Young Patients Treated With Inhaled Glucocorticoids. Lancet. 1993; 342:776–778. [PubMed: 8103877]

34. Phelan M. Beclomethasone Mania. Br J Psychiatry. 1989; 155:871–872. [PubMed: 2620226]

35. Dg-Bn Meyboom, Rh. Budesonide And Psychic Side Effects. Ann Intern Med. 1988; 109:683.

36. Lw Connett G. Inhaled Budesonide And Behavioural Disturbances. Lancet. 1991; 338:634–635.

37. Cg Lewis, Ld. Psychosis In A Child Inhaling Budesonide. Lancet. 1983; 2:634.

38. Ba Wilson, Am; Jung, Rt; Lipworth, Bj. Asthma And Cushing's Syndrome. Chest. 2000; 117:593–594. [PubMed: 10669710]