Respiratory Medicine (2006) **100**, 1307–1317

respiratoryMEDICINE

REVIEW

Systemic side effects of inhaled corticosteroids in patients with asthma

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Received 23 November 2005; accepted 25 November 2005

KEYWORDS
Adrenal suppression;
HPA-axis function;
Osteoporosis;
Growth velocity;
Skin thinning;
Cortisol

Summary Asthma is a complex disease of the respiratory tract associated with chronic inflammation in which an intricate network of cells and cellular factors plays a major role. Asthma is one of the most common chronic diseases, with an estimated 300 million cases worldwide, imposing a considerable burden on society in morbidity, quality of life, and healthcare costs. Inhaled corticosteroids (ICSs) form the gold standard, first-line therapy in the effective management of persistent asthma and reduce morbidity and mortality from asthma. However, long-term use of high-dose ICS therapy has potential to cause systemic side effects—impaired growth in children, decreased bone mineral density, skin thinning and bruising, and cataracts. Hypothalamic–pituitary–adrenal-axis suppression, measured by serum or urine cortisol decrease, correlates with the occurrence of systemic side effects of high-dose ICSs. Therefore, cortisol may be a relevant surrogate marker to identify the potential for adverse effects from ICS therapy. Ciclesonide is a new generation ICS with demonstrable safety and efficacy in the treatment of asthma. The unique pharmacologic characteristics of ciclesonide, such as reduced local adverse effects, lack of cortisol suppression, and the option for once-daily dosing, may improve compliance with therapy and allow long-term use of ICSs without fear of systemic adverse effects.

Contents

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doi:10.1016/j.rmed.2005.11.020

Introduction

Asthma is a complex disease that exhibits many clinical phenotypes in both adults and children.[1] The major characteristics of asthma include a variable degree of airflow obstruction, bronchial hyperresponsiveness, and airway inflammation.[2] The chronic inflammation associated with asthma involves an intricate network in which a number of cells and cellular factors play a major role. The presence of chronic inflammation in the airways leads to an increase in recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. These episodes are typically associated with extensive but variable airflow obstruction that may be reversible either spontaneously or with treatment. Although asthma begins most often in childhood and adolescence, it can develop at any time in life. A cross-sectional analysis of a group of patients with severe asthma indicated that there exists a phenotypic difference between patients with early onset and late-onset disease[3]; therefore, differentiating asthma by age at onset and the presence or absence of eosinophils may be beneficial in identifying asthma phenotypes that could benefit genetic and therapeutic studies.

Asthma is among the most common chronic diseases in the world, and the incidence has increased in the past 20 years, especially among children. An estimation of worldwide asthma prevalence suggests a trend of an increasing number of cases in developed nations. However, the lower incidence reported from developing or underdeveloped countries may represent a lack of awareness of the disease or the lack of well-developed medical care.[2,4] An estimated 300 million people worldwide currently suffer from asthma, and an additional >100 million persons are likely to suffer from this disease by the year 2025.[5] Asthma imposes a considerable burden on society in morbidity, quality of life, and healthcare costs.[6] In the US, an estimated $9.4 billion was spent on asthma-related direct costs, and the indirect costs from lost work productivity amounted to $4.6 billion, for a total of $14.0 billion in the year 2002.[7] A substantial proportion of family income, in a range of 5.5–14.5% in the US, has been attributed to the cost of medical treatments for asthma, whereas the cost of asthma treatment in India is 9% of per capita annual income.[5] Asthma is one of the leading causes for hospital admission in children in the UK, with more than 75,000 asthma-related emergency hospital admissions each year. With approximately 4 million asthma consultations and 1500 deaths from asthma each year, asthma exhausts £2.5 billion in healthcare costs in the UK.[5]

A wide array of pharmacologic therapies have been developed to prevent and control asthma symptoms, reduce the frequency and severity of asthma exacerbations, and reverse airflow obstruction.[8] Quick-relief or reliever medications used for asthma include short-acting β_2-agonists, anticholinergics, and systemic corticosteroids. Long-term preventive or controller medications used to treat asthma are corticosteroids, cromolyn sodium, nedocromil, long-acting β_2-agonists, methylxanthines, leukotriene modifiers, and immunoglobulin E antibody blocker (omalizumab).[5,8,9] Glucocorticosteroids are the most potent and consistently effective anti-inflammatory agents for effective long-term management of asthma. Inhaled corticosteroids (ICS) are the first-line treatment of choice for persistent asthma. Clinical studies have shown that ICS significantly reduce airway hyperresponsiveness, effectively prevent acute exacerbations, improve lung function, and decrease symptom severity.[10] The efficacy of ICS in reducing airway inflammation and hyperresponsiveness has been the major factor behind the widespread use of these agents as initial therapy in the treatment of moderate to severe asthma.[11,12] The national and international guidelines for asthma management currently recommend ICS as the first-line therapy at low doses for mild persistent asthma and as the preferred therapy at medium doses with long-acting β_2-agonists for moderate asthma.[2] High doses of ICS are only recommended for patients in whom persistent asthma is inadequately controlled even after combined treatment with medium-dose ICS and long-acting inhaled β_2-agonists. However, high-dose ICS use may be associated with systemic side effects including osteoporosis, reduced growth velocity in children, skin thinning, cataracts, and

Table 1 Potential local and systemic side effects of inhaled corticosteroids.

Local adverse effects	Systemic side effects
Pharyngitis	Suppressed HPA-axis function
Dysphonia	Adrenal crisis (with insufficiency)
Reflex cough	Suppressed growth velocity in children
Bronchospasm	Decreased lower-leg length in children
Oropharyngeal candidiasis	Reduced bone mineral density
	Suppressed HPA-axis function
	Bone fractures
	Osteoporosis
	Skin thinning
	Skin bruising
	Cataracts
	Glaucoma

HPA = Hypothalamic–pituitary–adrenal.

glaucoma.[11,13,14] Local side effects are also commonly associated with ICS, including oropharyngeal candidiasis, dysphonia, reflex cough, bronchospasm, and pharyngitis.[11,13] A summary of potential side effects caused by ICS is shown in Table 1. The objectives of this review are to discuss clinically relevant and meaningful systemic side effects of ICS, with an emphasis on the effect of long-term adrenal suppression.

Systemic side effects of inhaled corticosteroids (ICS)

Although the prevalence of systemic side effects of ICS is lower in comparison with systemic corticosteroids, high-dose ICS use has the potential to cause systemic side effects. Systemic exposure of ICS is directly related to the development of side effects. The amount of an inhaled or nasal corticosteroid that reaches the systemic circulation is the sum of the drug that is available after absorption across the lungs or nasal mucosa and from the gastrointestinal tract. The fraction of the drug that is deposited in the mouth will be swallowed, and oral bioavailability is determined by its absorption from the gastrointestinal tract and the degree of first-pass metabolism in the liver.[15] Because most of the drug deposited in the airways will eventually also be absorbed into the systemic circulation, pulmonary bioavailability also plays a role in the potential of an ICS to cause systemic effects. A reduction in the oropharyngeal deposition of ICS can be achieved by using a spacer device with a metered-dose inhaler (MDI), by mouth washing, or by using dry-powder inhalers,[14] but the presence of electrostatic charge on plastic devices[16] and the bulkiness of spacers are some of the drawbacks that could contribute to decreased compliance. Therefore, an ICS with durable, lung-targeted activity and low systemic exposure would have a theoretical advantage over currently available therapies for persistent asthma. In addition, pharmacokinetic parameters such as high lung deposition, high receptor binding, long pulmonary retention, and high lipid conjugation would improve or maintain the efficacy of such an ICS.[17]

Pharmacokinetic parameters such as rate of systemic clearance, volume of distribution, half-life, and accumulation also contribute to overall systemic exposure. Concomitant use of other ICS may play important causal roles in systemic side effects by pharmacologic interaction or increased total steroid load. The risks associated with systemic ICS exposure have been extensively studied and reviewed.[11,13–15,18,19] These systemic side effects, including osteoporosis, growth retardation, posterior subcapsular cataract formation, glaucoma, and skin thinning and bruising, are thought to be related to hypothalamic–pituitary–adrenal (HPA)-axis suppression.[14,19]

HPA-axis suppression

The most serious adverse effect of ICS use is adrenal crisis after complete suppression of HPA-axis function.[15,20] Corticosteroids can exert HPA-axis suppression by down-regulating corticotrophin (adrenocorticotropic hormone) production by the same feedback-inhibition loops that control endogenous glucocorticoid production, thus leading to adrenal suppression.[20] Although several studies have suggested that adrenal insufficiency after ICS therapy will rarely lead to acute adrenal crisis, a recent survey from the UK suggests that the use of ICS in excess of the currently recommended guidelines is associated with greater risk.[21] This study reported adrenal crisis in 33 patients (of 2912 questionnaires) who had received ICS (500–2000 μg/day), of whom 91% received fluticasone propionate and 3% received fluticasone propionate and budesonide.

Several studies have investigated HPA-axis function after ICS therapy (Table 2).[21–30] Although study designs differ in that studies were either uncontrolled, did not consider previous oral corticosteroid therapy, were of inconsistent

Table 2 Summary of selected studies on HPA-axis suppression in ICS therapy.

Reference	Patients	Adrenal assessment	Study design	ICS, dose and duration	Outcome
Grove et al.[22]	9 healthy subjects	Morning cortisol and tetracosactrin test	Randomized, single-blind, crossover study with 1-week washout between treatments	Budesonide 800 μg/day for 1 week, then 1600 μg/day for 1 week or fluticasone propionate 750 μg/day for 1 week, then 1500 μg/day for 1 week	Significant reduction in post-tetracosactrin serum cortisol ($P<0.05$) No change in morning cortisol No difference between fluticasone propionate and budesonide
Broide et al.[23]	46 asthmatic patients	Cortisol, low-dose ACTH test	Cortisol measurement following ACTH stimulation for assessment of adrenal function and detection of mild adrenal insufficiency	6-month treatment of patients with beclomethasone (mean daily dose 482 ± 42 μg) or budesonide (mean daily dose 507 ± 62 μg)	Low-dose ACTH test revealed mild adrenal insufficiency
Clark et al.[24]	10 stable asthmatic children with FEV_1 of 81.6% predicted being treated with ⩽400 μg/day ICS	12-h urine cortisol. Creatinine excretion	Placebo-controlled, single-blind, randomized crossover design	Single doses of budesonide or fluticasone propionate (400, 800, and 1250 μg).	12-h urine cortisol was suppressed by all doses of fluticasone propionate compared with placebo Budesonide did not show suppression at any dose.
Nielsen and Dahl[25]	66 asthmatic adults Patients were clinically stable, using ICS and hyperresponsive to methacholine.	24-h urinary cortisol Plasma cortisol	Double-blind, randomized, three consecutive 2-week treatments	Fluticasone propionate (500, 1000, or 2000 μg/day Budesonide 800, 1600, or 3200 μg/day	Fluticasone propionate-treated group had significantly higher 24-h urinary cortisol levels compared with budesonide group ($P<0.01$)
Martin et al.[26]	156 corticosteroid-naive asthmatic patients; all subjects were post-pubertal; FEV_1 between 65% and 90% predicted	Hourly plasma cortisol and 12- and 24-h urine cortisol	1-week doubling-dose design for 6 ICS and matched placebos; four doses in total	Beclomethasone (168–1344 μg/day) Budesonide (200–1600 μg/day) Flunisolide (500–4000 μg/day) Fluticasone propionate (DPI, 100–800 μg/day and CFC-MDI, 88–704 μg/day). Triamcinolone (800–6400 μg/day)	Budesonide DPI showed significant dose-response for the 12-h daytime, 12-h nighttime, and 24-h urine cortisol Fluticasone propionate DPI showed significant dose-response for 12-h daytime and 24-h measurements and fluticasone propionate-CFC MDI for 12-h nighttime urinary cortisol Other ICS did not show significant urinary cortisol dose–response
Todd et al.[21]	Questionnaires sent to 2912 patients; 33 met diagnostic criteria	HPA-axis function tests (not specified)	Questionnaire and follow-up using diagnostic criteria for presence of adrenal crisis	33 patients were treated with 500–2000 μg/day ICS; 91% fluticasone propionate, 3%	Fluticasone propionate was associated with 94% of cases of adrenal crisis

				fluticasone propionate or budesonide, and 6% beclomethasone	Study suggested that fluticasone propionate should not be used in excess of 400 μg/day in children
Chapman et al.[27]	329 adults with persistent asthma.	Serum and 24-h urinary cortisol.	Placebo-controlled, double-blind, parallel-group study with 2-week baseline period	Ciclesonide 160 μg, 640 μg (ex-actuator dose, equivalent to 200 and 800 μg ex-valve, respectively), or placebo once daily in the morning for 12 weeks	Serum and 24-h cortisol were unaffected by ciclesonide treatment
Derom et al.[28]	26 patients with asthma ($FEV_1 \geqslant 60\%$ predicted)	Plasma and 24-h urinary cortisol	Double-blind, double dummy, randomized, placebo-controlled study with 6-period crossover design with 3–12-week washout between treatments	Ciclesonide 320 μg, 640 μg (ex-actuator dose, equivalent to 400 and 800 μg ex-valve, respectively) once daily in the evening, ciclesonide 640 μg twice daily or fluticasone propionate 440 and 880 μg (ex-actuator dose, equivalent to 500 and 1000 μg ex-valve, respectively) twice daily, or placebo for 9 days	Fluticasone propionate caused significant decrease (29% and 59%; $P = 0.0003$ and $P = 0.0001$, vs placebo for 440 μg and 880 μg, respectively) in plasma cortisol and a dose-dependent decrease (44% and 69%; $P = 0.0001$ vs placebo for 440 and 880 μg, respectively) in urinary cortisol compared with placebo Ciclesonide did not significantly affect plasma or urinary cortisol secretion compared with placebo
Hansel et al.[29]	684 patients with persistent asthma	24-h urinary cortisol	Randomized, parallel-group, double-blind (ciclesonide), open-label (budesonide) with 1–4-week run-in period	Ciclesonide 80 μg or 320 μg (ex-actuator dose, equivalent to 100 μg or 400 μg ex-valve, respectively) once daily morning or budesonide 200 μg twice daily for 12 weeks	Mean urinary cortisol excretion was comparable with baseline for both ciclesonide doses, but was significantly reduced with budesonide ($P < 0.05$).
Pedersen et al.[30]	556 children with asthma (FEV_1 between 50% and 90% predicted)	24-h urinary cortisol	Randomized, parallel-group, double-blind study with 2–4-week baseline period	Ciclesonide 80 μg (ex-actuator dose, equivalent to 100 μg ex-valve) twice daily or fluticasone propionate 88 μg (ex-actuator dose, equivalent to 100 μg ex-valve) twice daily, for 12 weeks	24-h urine cortisol levels (adjusted for creatinine) increased in patients treated with ciclesonide or fluticasone propionate, but the increase was statistically significant only in patients treated with ciclesonide ($P < 0.05$)

ACTH = adrenocorticotropic hormone; FEV_1 = forced expiratory volume in 1 s; DPI = dry powder inhaler; CFC-MDI = chlorofluorocarbon metered-dose inhaler; ICS = inhaled corticosteroids.

treatment duration, employed a variety of inhaler types, or used different methods to assess HPA-axis suppression, these studies demonstrate that HPA-axis suppression occurs after high-dose ICS therapy. Many studies performed in healthy adults revealed HPA-axis suppression compared with baseline.[22,31] Some studies in asthmatic patients with normal HPA-axis function have also revealed dose-related cortisol suppression.[24] Therefore, HPA-axis suppression exists in normal individuals and asthmatic patients treated with high-dose ICS, but the extent of HPA-axis suppression is likely dependent on the dose, duration, and timing of corticosteroid administration.[32] However, several clinical studies have shown that ciclesonide, a nonhalogenated ICS,[33] has no appreciable effect on cortisol secretion. Short-term and long-term studies with ciclesonide 160–640 μg/day in the morning or evening did not suppress serum or 24-h urinary cortisol.[27,34–36] Because ciclesonide does not cause significant cortisol suppression, it is unlikely that ciclesonide poses a risk for other systemic side effects that are also thought to be related to HPA-axis suppression, unlike other ICS therapy.

To develop a dependable method for evaluating systemic bioavailability, a recent study compared 6 ICS preparations.[26] The authors concluded that a comparison of ICS should be based on the effective dose, rather than on the number of micrograms. Further studies along these lines could be helpful in assessing the therapeutic index of various ICS. Outcomes from several studies suggest that low to medium ICS doses may disturb basal cortisol secretion in adults and children, although the clinical relevance of this alteration is unclear. Biochemical studies also suggest that high-dose ICS may lead to adrenal suppression in children.[37] Although the benefit of ICS clearly outweighs the risk of therapy, use of ICS in children with early asthma onset is a particular concern because the duration of therapy correlates with the extent of adrenal suppression. Therefore, it is important to titrate ICS dose to the effective dose because even low to medium doses of ICS may perturb basal cortisol level, a marker of adrenal suppression. Finally, HPA-axis suppression may serve as a sensitive and quantifiable surrogate marker for potential systemic side effects of ICS.

Measures of HPA-axis suppression

Many standardized methods that use static or dynamic conditions are available for evaluating HPA-axis suppression (Table 3).[38] Static tests measure cortisol levels in the morning, the circadian rhythm of cortisol, and free urine cortisol excretion. Dynamic tests measure the adrenal response after the stimulation of the gland. The corticotrophin adrenocorticotropic hormone test evaluates the adrenal reserve, whereas insulin and metyrapone tests evaluate the integrity of the whole HPA-axis, both adrenal and pituitary.

Because plasma cortisol levels vary widely among individuals, baseline levels for each patient ideally should be obtained before starting ICS treatment. To obtain consistent results, the morning cortisol level determinations should be performed at the same time and confirmed by repeated testing.[39] A careful evaluation of data is necessary to detect any underlying clinical effects or HPA-axis suppression.[14,40] In addition, measurement of 24-h urinary free cortisol excretion has been proposed as a better method for assessing basal cortisol levels in a dose–response manner.[19,25,26,41] However, similar to morning serum cortisol measurement, urinary free cortisol measurement may not be predictive of clinical adrenal suppression. Because the technique is noninvasive, it is primarily useful in determining cortisol levels in children.[13]

Table 3 Standard methods available to evaluate HPA-axis suppression.

Method	Normal range (mmol/L)
Plasma cortisol level	0800 h: 138–635 1600 h: 83–413 2000 h: ⩽50% of 800 h
Urinary cortisol (24-h urine)	Children: 5.5–74 Adolescents:14–152
Corticotrophin (ACTH) test	An increase of 200 in plasma cortisol level or a level of 500
Low-dose corticotrophin (ACTH) test	An increase of 200 in plasma cortisol level or a level of 500
Insulin-induced hypoglycemia	Cortisol level ⩾550

ACTH = adrenocorticotropic hormone.
Adapted with permission from Salvatoni et al.[38] (Table V on p. 358).

Although the morning serum cortisol concentration (between 8 and 9 AM) and short corticotrophin (cosyntropin) stimulation tests have been the standard tests for assessing basal cortisol secretion and HPA-axis responsiveness, respectively,[20] studies suggest that these tests may not be sensitive enough to detect low levels of HPA-axis suppression caused by ICS.[23] The standard 250-μg cosyntropin test uses a supraphysiologic dose of cosyntropin and may miss mild adrenal suppression. Therefore, low-dose cosyntropin tests (with 0.5 $\mu g/m^2$ cosyntropin) are more physiologic and are therefore being advocated.[23] The low-dose cosyntropin test has been thought to correlate well with the insulin-induced hypoglycemia test, which is still widely considered in the definitive study of HPA-axis integrity. However, compared with the insulin-induced hypoglycemia test, the low-dose cosyntropin test has shown fewer false-negative results.[42] Because the test is relatively new, some investigators have suggested that if the results of this test are not definitive, it should be followed by an insulin-induced hypoglycemia or metapyrone test.[20] It is noteworthy that, compared with other HPA-axis function measures, both insulin-induced hypoglycemia or the metapyrone test are technically difficult, require hospitalization, and are more hazardous and expensive than cortisol monitoring.

Because of the availability of a variety of laboratory tests for the evaluation of cortisol, it is important to use a sensitive and feasible method that could be adopted in a clinical laboratory. Adopting such a practice in the clinic could help optimize ICS use, thus increasing efficacy and safety of ICS in the management of asthma.

Growth suppression

Because ICS treatment is currently recommended for children of all ages with persistent asthma, the potential effect of ICS on children's growth is a crucial consideration. Severe asthma or concomitant atopy may negatively affect growth in children.[8,11] ICSs to treat asthma are likely to be a long-term therapy, especially in children,[43] and long-term use of ICS in children may potentially lead to adverse effects on growth by suppression of HPA-axis function. However, because several other factors contribute to normal growth, including genetic background and individual variations in onset of puberty, it is difficult to assess the effect of ICS on growth in children with asthma.

Growth has been commonly evaluated using knemometry to measure changes in lower leg length as an index of short-term growth, usually over a 2–4-week period. A decrease in short-term lower-leg growth velocity demonstrates the systemic activity of ICS. In a double-blind, randomized, 2-week crossover trial in 17 asthmatic children, knemometry and other markers of growth indicated greater growth suppression by beclomethasone dipropionate (BDP) than by fluticasone propionate.[44] In another study, no significant difference in the lower-leg growth rate was found between budesonide and fluticasone propionate at high doses (400 μg/day).[45] Finally, both fluticasone propionate and budesonide caused a significant slowing of lower-leg growth length compared with placebo in asthmatic children ages 1–3 years.[46] In contrast, ciclesonide 40–160 μg/day showed no effect on the short-term lower-leg growth rate among 24 children (age 6–12 years) with asthma.[47]

Long-term studies of duration greater than 12 months suggest that asthmatic children treated with ICS for this duration ultimately achieve near-normal adult final heights. The Childhood Asthma Management Program (CAMP) study compared the long-term effects of therapy of inhaled budesonide (400 μg/day), nedocromil (16 mg/day), or placebo. Children treated with budesonide grew at a slower rate during the first year compared with those treated with nedocromil or placebo; however, there was no difference in growth velocity in subsequent years.[48] A long-term cohort study demonstrated no difference in attained adult height between age- and sex-matched children with asthma who were either treated or not treated with ICS. In addition, there was no difference in attained height between asthmatic and nonasthmatic children.[49] These results were confirmed by a study[50] comparing adult height attained by asthmatic patients treated with budesonide (412 μg mean daily dose for 9.2 years), asthmatic children who were never treated with ICS, and a small group of healthy, nonasthmatic siblings. There was no apparent difference in adult height among the study groups. Taken together, the long-term studies suggest that, overall, asthmatic children treated with ICS attain near-normal adult height,[18] although individual variations could still exist.[51]

Bone density and osteoporosis

Glucocorticoids reduce bone formation and increase bone resorption by direct actions on osteoblasts and osteoclasts. These phenomena can lead to bone calcium loss via urine and decreased vitamin D-mediated calcium absorption

in the gut, thereby decreasing total body calcium stores. Therefore, ICS therapy during childhood, a critical time for bone development, could adversely affect bone mass and may predispose asthmatic children for osteoporosis during adulthood.[37,52] Several studies have measured bone mineral density (BMD) in growing children who have asthma to determine the effects of ICS on BMD; however, the results are difficult to interpret because of the expected constant change in BMD throughout childhood. A study of 48 asthmatic prepubertal children treated with either BDP or budesonide indicated a reduction in BMD.[52] However, a study of 15 asthmatic children treated with BDP (200–450 μg/day) for 4–60 months revealed BMD equivalent to that of the control subjects.[53] In children with moderate to severe asthma (age range, 5–10 years; mean age, 6.7 years) treated with 200 μg/day of fluticasone propionate or 400 μg/day BDP for 82 weeks, neither BDP or fluticasone propionate had an effect on BMD.[54] Finally, the CAMP study indicated no difference in BMD for budesonide therapy compared with nedocromil or placebo therapies.[48] Such studies suggest that ICS therapy at low to moderate doses is not associated with a reduction in BMD in children. However, prolonged HPA-axis suppression and any effect on bone metabolism in children administered high-dose ICS remain to be examined.

Several studies have investigated the effects of ICS on BMD in adults with asthma. A cross-sectional study of 1673 adults (age range, 56–91 years) suggested that women receiving ICS therapy had modest decreases in BMD at the ultradistal radius, hip, and spine compared with women who received no ICS treatment or women receiving oral corticosteroids. However, there was no significant difference in BMD between untreated men and men treated with oral corticosteroids or ICS.[55] The results of two studies in patients ages 18–50 years treated with mometasone furoate 200 or 440 μg twice daily for 2 years were mixed, with the lower-dose study demonstrating significant reductions in lumbar spine BMD, whereas the higher-dose study reported no statistically significant difference in lumbar spine BMD versus placebo.[56] Treatment of 19 nonsmoking asthmatic women (age range, 40–63 years; mean age, 53 years) and 19 similar-age healthy, nonsmoking women with BDP (1000 μg/daily) for 1 year resulted in no significant changes in BMD.[57] Conversely, bone-mass studies in three groups of adults with asthma indicated that BMD was significantly lower in groups receiving ICS therapy (BDP; 1000–2000 μg/day for 1 year) or ICS and low-dose prednisolone therapy compared with BMD in asthmatic patients who had never received ICS or systemic corticosteroids.[58] This study suggested that asthmatic patients treated with high-dose inhaled BDP and intermittent systemic corticosteroids experienced a reduction in vertebral bone density. Notably, the degree of bone loss was similar in patients treated with ICS therapy alone and in patients treated with continuous low-dose systemic corticosteroids. A cross-sectional study of 196 adult asthma patients (age range, 20–40 years) with a mean duration of 6 years (range, 0.5–24 years) of ICS treatment indicated a negative relationship between cumulative ICS dose and BMD of the lumbar spine and femoral neck.[59] This study also indicated that doubling the dose of ICS resulted in a decrease in lower-spine BMD (0.16 standard deviation). BMD of a patient receiving ICS treatment of 2000 μg/day for 7 years will have BMD that is 1 standard deviation lower than that of a patient on 200 μg/day for 1 year, indicating that a higher ICS dose could double the risk of fracture. Therefore, long-term ICS use results in BMD reductions that could lead to increases in fractures in adults.

Cataracts and glaucoma

Although the use of systemic corticosteroids poses an increased risk for cataracts, it has been difficult to establish a definitive link between ICS therapy and cataract formation. The occurrence of posterior subcapsular cataracts with ICS and oral steroid therapy was studied in a cross-sectional survey.[60] The results indicated that 27% of the 48 adult patients had subcapsular cataracts. The increased incidence correlated with the daily dose and duration of oral prednisolone but was not associated with the dose or duration of ICS use. However, in a population-based, cross-sectional study of 3654 older adult patients (age range, 49–97 years) in Australia, there was an association between ICS use and posterior subcapsular and nuclear cataracts.[61] The CAMP research group also studied the development of posterior subcapsular cataracts associated with long-term budesonide, and only 1 child developed evidence of cataract at the end of the 6-year study period.[48] Therefore, the risk of subcapsular and nuclear cataract development related to ICS use seems minimal in asthmatic children, although the risk may be greater in older patients. Therefore, no firm link between cataract formation and ICS use has been made to date, and longer follow-up regarding this important potential adverse effect seems warranted.

Studies to link the association of glaucoma to ICS therapy include only a few isolated case reports. A prospective study of 187 patients with various pulmonary conditions and no documented history of glaucoma evaluated the risk of elevation of intraocular pressure in patients after the initiation of ICS therapy.[62] The results indicated no significant increase in intraocular pressure in these patients; hence, they suggest that the risk of glaucoma after ICS therapy is very low. Garbe et al.[63] conducted a case-control study involving more than 40,000 patients to investigate the association of ICS therapy with increased risk of ocular hypertension or open-angle glaucoma. Therapy with ICS was not associated with increased risk of either. However, the authors suggested that long-term ICS use may increase the risk and that monitoring of ocular pressure may be necessary in patients on prolonged ICS therapy. Published results concluded that the risk of glaucoma following ICS therapy is most likely small, and future studies might be helpful in defining a definitive link between ICS use and glaucoma in the elderly.

Skin thinning and bruising

Several studies indicate that skin thinning and skin bruising, common adverse effects of long-term oral corticosteroid use, can be linked to ICS therapy. A cross-sectional study of 68 patients treated for chest diseases showed that patients treated with high-dose ICS had significantly thinner skin (15–19% thinner compared with controls).[64] The prevalence of easy bruising in patients treated with ICS in a respiratory clinic and in a control group without ICS therapy was studied in 406 patients.[65] The results suggested that ICS therapy, especially with high doses, increased the risk of easy bruising. Although sex was indicated to be a factor in this study because women reported easy bruising at a higher frequency versus men, men treated with ICS also had a higher relative risk for bruising than women. A Finnish study of asthmatic patients suggested that inhaled budesonide decreases skin collagen synthesis within a short period of time (6 weeks).[66] Roy et al.[67] studied the prevalence of skin bruising in relation to adrenocortical function and ICS therapy in 100 asthmatic patients. Adrenocortical function tests indicated that a minority of patients had lower urinary or blood cortisol levels, which was evident in patients with skin bruising. In addition, the likelihood of skin bruising was common in women receiving ICS therapy for asthma, with an increased occurrence of skin bruising in older women with asthma. On the basis of these studies, it appears that there is an increased rate of skin thinning and bruising in patients treated with ICS. The overall risk is likely related to dose, duration of use, and sex.

Summary

Concerns regarding potential systemic side effects may limit the use of ICS doses that are effective for long-term asthma management. Therefore, an ICS with high efficacy and low systemic bioavailability may ultimately result in fewer systemic side effects and would be desirable. ICSs can reach systemic circulation either by deposition in the oropharynx, where they are swallowed and absorbed into the systemic circulation from the gastrointestinal tract, or by deposition in pulmonary airways. Therefore, an ICS with efficacy comparable with the existing gold standard and a low risk for systemic effects may reduce concerns about systemic side effects and improve compliance with—and thus efficacy of—ICS maintenance therapy. Ciclesonide, a nonhalogenated ICS, possesses key pharmacokinetic and pharmacodynamic characteristics that yield high efficacy and low risk for systemic exposure. Because ciclesonide does not cause significant cortisol suppression, it is unlikely that ciclesonide poses a risk for other systemic side effects that are thought to be related to HPA-axis suppression. However, no data for ciclesonide are available for other systemic side effects such as skin thinning, bruising, and fracture, and studies are necessary to further investigate long-term effects.

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