REVIEW

Inhaled corticosteroids in childhood asthma: the story continues

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Abstract Inhaled corticosteroids (ICS) are the most effective anti-inflammatory drugs for the treatment of persistent asthma in children. Treatment with ICS decreases asthma mortality and morbidity, reduces symptoms, improves lung function, reduces bronchial hyperresponsiveness and reduces the number of exacerbations. The efficacy of ICS in preschool wheezing is controversial. A recent task force from the European Respiratory Society on preschool wheeze defined two different phenotypes: episodic viral wheeze, wheeze that occurs only during respiratory viral infections, and multiple-trigger wheeze, where wheeze also occurs in between viral episodes. Treatment with ICS appears to be more efficacious in the latter phenotype. Small particle ICS may offer a potential benefit in preschool children because of the favourable spray characteristics. However, the efficacy of small particle ICS in preschool children has not yet been evaluated in prospective clinical trials. The use of ICS in school children with asthma is safe with regard to systemic side effects on the hypothalamic–pituitary–adrenal axis, growth and bone metabolism, when used in low to medium doses. Although safety data in wheezing preschoolers is limited, the data are reassuring. Also for this age group, adverse events tend to be minimal when the ICS is used in appropriate doses.

Keywords Inhaled corticosteroids · Asthma · Children · Preschool · Safety · Wheeze

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Introduction

Inhaled corticosteroids (ICS) are the cornerstone of asthma treatment in adults and children. They remain the most effective anti-inflammatory drugs for the treatment of persistent asthma. Since their introduction in the early 1970s, no other equally effective drug for asthma treatment has become available, and this will probably remain so for the foreseeable future. Treatment with ICS has decreased asthma mortality and morbidity [61]. In addition, treatment with ICS reduces symptoms, improves lung function, reduces the degree of bronchial hyperresponsiveness (BHR) and reduces the number of exacerbations [1–3]. ICS treatment improves the burden of asthma by decreasing the number of nocturnal awakenings due to respiratory symptoms, by reducing school absence and, especially valuable for children, by helping to enable participation in sports and other social activities [60].

The goal of asthma therapy for children is to achieve asthma control by optimising lung function, reducing day and night time symptoms, reducing limitations in daytime activities and the need for reliever treatment and by reducing asthma exacerbations [27]. However, especially in children, it is of importance to achieve control with a minimum of side effects of medication.

Guidelines from all countries advocate the use of ICS for the treatment of persistent asthma. Due to the efficacy of ICS as a class, low- to medium-dose ICS treatment outweighs the potential risks of adverse effects [53]. Recent Global Initiative for Asthma Guidelines recommend low-dose ICS (low-to-medium dose 100–200 μg beclomethasone dipropionate (BDP) equivalent twice daily or 125–250 μg fluticason twice daily) therapy when asthma symptoms requiring a short-acting beta$_2$-agonist occur more than once per week (but less than daily; step 2) and as

baseline therapy with various adjunctive therapies for more severe disease (steps 3 and 4) [27]. In children 5 years of age or younger, low-dose ICS is advocated in partly controlled asthma, with a doubling of the dose for those with uncontrolled asthma or asthma that is partly controlled on a low-dose of ICS (see Fig. 1).

ICS therapy for asthma, especially for children, has changed substantially since the introduction of the first ICS, BDP, in the early 1970s, followed soon thereafter by budesonide (BUD). Over the last two decades, a number of novel ICS, such as fluticasone propionate (FP), as well as the small particle ICS ultrafine hydrofluoroalkane (HFA)-BDP and ciclesonide, have entered the market. In addition to improvements in the ICS molecules available for the treatment of asthma, our understanding of the importance of the deposition characteristics of these drugs in determining safety and efficacy has increased. Finally, there have been significant advances in inhaler technology, and this too can impact the effectiveness of an ICS. The purpose of this review, therefore, is to provide an updated overview of relevant studies in children of school age as well as in preschool children with respect to the efficacy, safety and lung delivery of ICS.

History

In 1936, cortisone, initially called compound E, was for the first time extracted from the renal cortex by Edward Kendal at the Mayo Clinic. In 1950, the first report on successful use of cortisone in asthma was published, followed soon thereafter by a confirmatory clinical trial [16,58]. Despite its apparent efficacy, it became obvious that the adverse effects following long-term treatment were substantial. Hypertension, diabetes mellitus, osteoporosis, obesity, facial mooning, acne, skin thinning and bruising, the development of glaucoma and, especially in children, growth retardation were some of the severe complications of this relatively new treatment option. Search for safer

compounds and safer modes of administration of corticosteroids led to the introduction of inhaled BDP in the 1970s, which, based on evidence from clinical trials, was administered four times per day, following initial approval. Subsequently, Willey et al. showed that twice daily administration of the new corticosteroid, BUD (200 μg twice daily), was as effective as four times daily therapy [74]. Based on these data, as well as patient preference, twice daily dosing became the standard regimen for all ICS with the exception of ciclesonide and budesonide in mild asthma, which can be administered by inhalation once daily. However, it is important to note that ciclesonide is not approved for once daily use in some countries such as the USA.

Inhaled corticosteroids also became the standard of care for the treatment of asthma in children after it had been convincingly demonstrated that treatment of the underlying airway inflammatory processes provided overall asthma control that was far superior to bronchodilator treatment alone. In children aged 7–16 years, Van Essen-Zandvliet et al. [67] showed that the effects of chronic treatment with BUD (100 μg administered three times per day for 22 months) was far superior to chronic treatment with the short acting β_2 adrenergic drug, salbutamol (200 μg administered three times per day), with respect to asthma symptoms, lung function, degree of BHR and frequency of exacerbations. Eight years later, these results were confirmed in a much larger population of school children (aged 5–12 year) in the USA with mild to moderate persistent asthma who received 200 μg budesonide, 8 mg nedocromil, or placebo twice daily for 4–6 years [64]. The results of these and other paediatric asthma studies provide a solid foundation for our current understanding of ICS and their role in the treatment of paediatric asthma, and one may conclude that inhaled corticosteroid treatment is very effective in school-aged children.

Despite the introduction of other classes of medications for children with asthma in the last decades, ICSs continue to be the recommended first-line maintenance therapy for

Fig. 1 Gina guidelines for children 5 years and younger

GINA Asthma management approach based on control for children 5 years and younger		
Asthma education, Environmental Control, as needed β2 agonists		
Controlled on as needed rapid-acting β2-agonists	Partly controlled on as needed rapid-acting β2-agonists	Uncontrolled or only partly controlled on as needed rapid-acting β2-agonists

Controller options		
Continue as needed rapid acting β2 agonists	Low dose inhaled corticosteroid	Double low-dose inhaled corticosteroid
	Leukotriene modifier	Low-dose inhaled corticosteroid plus Leukotriene modifier

paediatric asthma patients in numerous national and international asthma treatment guidelines. For example, inhaled, long-acting beta$_2$-agonists (LABA) were introduced approximately 20 years ago. Early studies with LABAs in children showed little or no benefit when these agents were added to a maintenance regimen that included an ICS [51,70]. A more recent systematic review in adults and children [54] showed that the addition of LABA to an ICS in patients who are symptomatic on low to high doses of ICS reduces the rate of exacerbations requiring systemic corticosteroids, improves lung function and asthma symptoms and reduces the use of rescue short-acting beta$_2$-agonists. However, when only paediatric studies were included in the analyses [55], the addition of a LABA to an ICS was not associated with a significant reduction in the rate of exacerbations requiring systemic corticosteroids but was associated with a significant improvement in lung function compared with an ICS alone. Similarly, compared with a double dose of ICS, the combination of a LABA and a lower dose of ICS did not significantly decrease the risk of exacerbations requiring oral corticosteroids, but it did result in significantly greater improvements in peak expiratory flow and caused significantly less growth impairment [55].

A major new class of asthma treatments introduced within the past 15 years belongs to the class of agents referred to as leukotriene-modifying drugs. As a class, these agents did not have a major impact on treatment outcomes in paediatric asthma. A dose of 400 μg/day of BDP or equivalent ICS appeared to be more effective than the usual approved doses of anti-leukotriene agents [23]. In addition, the use of anti-leukotrienes as add-on therapy to ICS leads, at most, to modest improvements in lung function, and overall asthma control often deteriorates when the ICS is tapered or discontinued [22].

Despite the introduction of other classes of asthma medication, ICS remain the most important anti-asthma therapy in school children with asthma.

Inhaled corticosteroids in preschool children

Population studies have shown that one in three children will have at least one episode of wheezing before they reach their third birthday, rising to almost one in two (50%) by age 6 [30,49]. Unfortunately, the ability to predict who among these children will have *transient* versus *persistent* problems is poor. As such, epidemiological data, such as these, has limited clinical applicability. In this regard, prospective studies in which subjects were also phenotyped using a number of different clinical measures (e.g., lung function, BAL, etc.) showed considerable overlap between these groups [13]. Therefore, at present, there are no

diagnostic tools that can reliably predict the development of asthma among wheezy infants.

Noisy breathing is common among infants. It is important to note that it is difficult for parents to recognise wheezing, and accurately identifying wheezing by medical history is virtually impossible, as the term is used by parents and doctors to describe a variety of symptoms [15]. Children with physician-confirmed wheezing have higher airway resistance than children with parent-reported wheeze [47]. It may be that physician-confirmed wheezing can become important as a predictor for the development of asthma at older age. We observed that preschool children with an increased specific IgE and who also wheezed had a substantially increased chance of developing asthma by the time they reached school age [25]. Unfortunately, in this study, wheezing was not reported by a physician. Devulapalli et al. demonstrated that a high severity score of obstructive airways disease by 2 years of age is a strong risk factor for, and may predict, current asthma at 10 years of age [19]. Bronchial biopsies obtained from infants with confirmed wheezing have shown increased thickness of the reticular basal membrane and significantly greater eosinophilic inflammation compared with samples from children with parent-reported wheezing or control subjects [59].

Early identification of asthma is mandatory in school children since early treatment in this age group can prevent exacerbations and deterioration of lung function. However, in preschool children, no such data are available. Recent early intervention studies with ICS in young children aimed at the prevention of asthma have shown no beneficial results with respect to the development of asthma [11,29,52], and the results of therapeutic studies are conflicting.

Episodic viral wheeze [13]

Episodic viral wheeze has been defined recently by a European Respiratory Society task force to describe children who wheeze intermittently and are well between episodes. The efficacy of ICS in the treatment for episodic viral wheeze in preschool children is controversial. The majority of asthma exacerbations in school-aged children are associated with viral infections [35], and this also holds true for the majority of wheezing episodes in preschool children [77]. Intermittent versus daily ICS treatment in children was reviewed by the Cochrane Airways Group [50]. Studies in children up to 17 years of age were included, but the review also contained studies conducted in preschool children. This review showed that children benefited from intermittent use of high-dose ICS (1,600–3,200 μg/day BDP or BUD) as evidenced by a reduction in the severity of symptoms. There was also a trend for

reduced requirements of oral corticosteroids. More recently, a controlled, randomised, double-blind clinical trial of 750 μg FP versus placebo twice daily in 129 children who were 1–6 year of age with recurrent virus-induced wheezing showed a reduction in the use of rescue oral corticosteroids in the FP-treated patients [24]. However, treatment with FP was associated with a smaller gain in height and weight. Among preschool children, no benefit was shown for continuous low-dose ICS treatment (400 μg/day BUD) with respect to a reduction in the number or the severity of wheezing episodes [75]. Finally, a double-blind, placebo-controlled, randomised interventional study, primarily designed to assess whether or not treatment with intermittent courses of inhaled budesonide (400 μg/day) versus placebo for 2 weeks during wheezing episodes could delay progression to persistent wheezing, did not show any benefit of ICS during the first 3 years of life [11].

Maintenance treatment with ICS in episodic viral wheeze in low-to-medium dosage seems not beneficial. Intermittent treatment with high-dose ICS during wheezing episodes has some beneficial effects but increases the risk of systemic side effects. An alternative possibility for this phenotype is treatment with montelukast, which reduced the rate of wheezing episodes in 549 preschool children with episodic viral wheeze by 32% compared to placebo [12].

Multiple-trigger wheeze [13]

Multiple-trigger wheeze has been defined recently by a European Respiratory Society task force to describe children who wheeze both during and outside discrete episodes. The treatment of preschool children with multiple-trigger wheeze with ICS appears to be more successful than that of children with episodic viral wheeze. Children with multiple-trigger wheeze often develop symp-toms after crying, laughter or exercise. Based on these findings, many believe that multiple-trigger wheeze resembles allergic asthma, but there is little direct evidence to support this. It remains unknown whether the histopathology of the airways from children with multiple-trigger wheeze resembles that of allergic asthma. However, a proportion of preschoolers with persistent wheeze do develop asthma in later life [49,78].

Kaditis et al. [37] and Castro-Rodriguez et al. [17] reviewed the literature on the efficacy of ICS in recurrent wheezing preschool children. Based on these systematic reviews, as well as a number of randomised, double-blind, placebo-controlled clinical trials published after this review was completed, it is concluded that continuous treatment with ICS decreases the number of days with symptoms among children with persistent wheezing, without preventing the need for hospitalisation [14] and had less wheezing/asthma exacerbations and improved their symptoms and lung function, respectively [17].

There is solid evidence that maintenance treatment with a low-to moderate dose of ICS decreases the number of days with asthma symptoms in children with multiple-trigger wheeze. However, Kaditis et al. [37] questioned whether the relative benefit of continuous treatment with ICS (approximately 5% fewer symptom-free days versus placebo) is clinically significant and outweighs the possible side effects. Montelukast improved symptoms and achieved a 30% reduction in exacerbations in 689 preschool children with multiple-trigger wheeze [41], but head-to-head comparisons with an inhaled corticosteroid are not available in the literature [7,13] (Table 1).

Newer, small particle ICS, such as ultrafine HFA-BDP aerosol (QVAR) and ciclesonide, may offer a potential benefit in preschool children. This resulted in a recommendation in the revised Dutch Paediatric Asthma Guidelines 2007 to treat children under 6 years with a small particle ICS [32]. This recommendation is primarily based on a

Table 1 Characteristics of episodic viral wheeze and of multiple-trigger wheeze

	Episodic viral wheeze	Multiple-trigger wheeze
Definition	Wheezing during discrete time periods, often in association with clinical evidence of a viral cold	Wheezing that shows discrete exacerbations but also symptoms between episodes
Triggers	Viral infections	Viral infections, tobacco smoke, allergen exposure, mist exposure, crying, exercise
Possible underlying factors	Pre-existent impaired lung function, tobacco smoke exposure, prematurity, atopy	Eosinophilic inflammation?
Continues treatment with ICS	Little or no benefit	Significant fewer days with symptoms
Treatment with montelukast	Moderate benefit	Moderate reduction in exacerbations
Long-term outcome	Declines over time (<6 year), can continue as episodic viral wheeze into school age, can change in multiple-trigger wheeze	Can continue as asthma into adulthood

model-deposition study that is outlined below. The average particle size is smaller [median mass aerodynamic diameter (MMAD) of both compounds is 1.1 μm], the velocity of the particles leaving the inhaler on actuation is slower, the duration of the spray is longer and the temperature of the spray is warmer compared with that of traditional inhalers [42]. As a result, a softer more gentle spray is produced, fewer particles impact on the oropharynx and more drug reaches the lung, particularly the small airways [43]. These improved delivery characteristics may be particularly relevant for young children in whom a greater proportion of airways are classified as small (i.e. <2 mm in diameter) and airways resistance is low [68].

In adults with asthma, ultrafine HFA-BDP aerosol provides equivalent asthma control at half the daily dose of conventional chlorofluorocarbon (CFC)-BDP [18]. Two clinical studies with ultrafine HFA-BDP were performed in school children with asthma [62,66]. The first was a 6-month, open-label, randomised clinical trial that confirmed that asthma control can be well maintained in children aged 5–11 years when switching from a conventional CFC-BDP metered dose inhaler (MDI) inhaled via a spacer to ultrafine HFA-BDP (administered via an Autohaler®) at doses as low as 100–200 μg/day [62]. A randomised controlled, double-blind, double-dummy clinical trial in school children aged 5–12 years with mild–moderate asthma showed that ultrafine HFA-BDP MDI and CFC-fluticasone MDI were equally effective in improving asthma control in children with mild–moderate asthma at the same daily dose and that the majority of children in both groups could reduce their daily dose to as low as 50 μg/day while maintaining good asthma control [66]. In 2008, a Cochrane Systemic Review compared ciclesonide with other inhaled corticosteroids in children and adults with asthma [48]. The majority of the studies were performed in asthma patients from 12 to 75 years of age. Three of the studies were performed in children, aged 6–11, 12–17 and 6–11 years, respectively [57,71,73]. In 6–11-year-old children, a randomised, double-blind, double-dummy, three-arm, parallel group study showed that once daily ciclesonide (80 or 160 μg daily) administered via a MDI without a spacer had a clinical effect similar to that of FP (100 μg twice daily) administered via a MDI [57]. The two other studies compared the efficacy of ciclesonide (320 and 160 μg once daily, respectively) with BUD (800 μg and 400 μg once daily, respectively). These studies were conducted over a period of 12 weeks in children with asthma ages 12–17 and 6–11 years, respectively, and the results showed similar efficacy with ciclesonide and BUD in a 1:2 dose ratio [71,74].

Unfortunately, the efficacy of small particle inhaled corticosteroids in preschool children has not yet been evaluated in prospective clinical trials. This is the reason that HFA-BDP in The Netherlands is registered from the age of 5 years and older. This is in contrast with the recommendation in the revised Dutch Paediatric Asthma Guidelines 2007 [32]. The only study that suggests that small particle ICS may have an advantage in very young children is an infant model study. In an anatomically correct model of the upper airway of a 9-month-old infant, the SAINT model [33], lung deposition of CFC-BDP (MMAD 3.5–4.0 μm) and ultrafine HFA-BDP (MMAD, 1.1 μm) was compared. The SAINT model was connected to a breathing simulator and a cascade impactor. This study showed that lung doses for ultrafine HFA-BDP were 25.4–30.7% over the range of tidal volumes evaluated (50–200 ml), while the lung doses for CFC-BDP ranged from 6.8% to 2.1% [34]. The deposition of the small particles was relatively independent of tidal volume, which may be a theoretical advantage in young children. This study suggests that ultrafine HFA-BDP will be delivered in an increased lung dose in preschool children compared with an ICS that has a higher MMAD. However, these data must be interpreted with the caveat that drug delivery for individual patients in clinical practice also depends on other factors such as the inhalation technique and the cooperation of the child (Table 2).

Adverse effects

Local adverse effects of inhaled corticosteroids, such as hoarseness as well as oral candidiasis, may cause serious discomfort in children, although these adverse effects are less common than in adults.

Due to the well-known adverse effects of systemic corticosteroids, there is general awareness of the potential for adverse systemic effects with ICS as well, especially when they are administered at high doses for extended periods of time. Adverse systemic effects of ICS have been reviewed extensively [8,39,40,44,45,56,65]. All corticosteroid actions are mediated through the stimulation of glucocorticosteroid receptors in the cytoplasm of cells throughout the tissues. However, there is widespread heterogeneity in both the efficacy as well as the systemic safety of ICSs among individuals with asthma, even when using the same doses of ICS. This variability in response is multifactorial and includes environmental and genetic factors [39].

Principal methods for reducing systemic activity include reducing the bioavailability of the ICS from the gastrointestinal tract and prolonging residence time of the ICS in the lung tissue. Improving drug delivery to the lungs by a better inhalation device may also result in higher systemic availability of the ICS. Therefore, the efficacy and adverse effects of an ICS are coupled with the delivery device. The

Table 2 Current knowledge on ICS	What is known	What is new	What is uncertain
	ICs are the cornerstone of asthma treatment	Early intervention with ICS does not prevent the development of asthma	VEW and MTW are distinct phenotypes
	ICS reduce symptoms, improve lung function and prevent deterioration of lung function over time, improves BHR, reduces exacerbations in school aged children	Phenotypes VEW and MTW	MTW=asthma
	ICS are safe in low to moderate dose	ICS in EVW not efficacious, but more effective in MTW	Physicians confirmed wheezing predictive for asthma
		MTW resembles asthma	No clinical studies with small particle ICS in preschool children
ICS inhaled corticosteroids, *VEW* viral episodic wheeze, *MTW* multiple-trigger wheeze, *BHR* bronchial hyperrespon-siveness		Parent reported wheeze is unreliable	No head to head studies ICS vs montelukast in preschool children

ICS molecule can be altered to reduce gastrointestinal absorption or enhance first-pass metabolism by the liver. Prolonged residence time in lung tissue can be achieved by increasing lipophilicity (e.g., mometasone furoate and fluticasone propionate) or by forming soluble intracellular esters (e.g., BUD and ciclesonide) [5]. However, all ICSs delivered to the lung have systemic activity that increases in a dose-dependent fashion [5].

HPA axis and inhaled corticosteroids

The primary systemic adverse effects of concern following ICS administration in children are suppression of hypotha-lamic–pituitary–adrenal (HPA) axis responsiveness, sup-pression of growth and osteoporosis [5]. Adverse effects of ICS on the skin (atrophy and bruising) and the eyes (glaucoma) are, in contrast to adults, uncommon in children. A number of measures have been used to assess systemic effects of ICS including effects on HPA axis function. The presence of exogenous glucocorticosteroids in the bloodstream will reduce the need for endogenous cortisol production. Consequently, measures of HPA axis activity, such as 24-h area under the curve cortisol concentrations and 24-h urinary free cortisol excretion, provide sensitive measures of HPA axis suppression. However, the more sensitive the measure, the more difficult it is to interpret its clinical significance [39]. Changes in 24-h area under curve for cortisol do not predict clinically relevant adverse effects [38], such as Cushing's disease or adrenal insufficiency/crisis, both of which are very significant clinical consequences of exogenous glucocorticoid administration. In children, clinical manifestations of adrenal suppression as a conse-quence of the use of ICS are extremely rare [34] and seem

to be related to the administration of very high doses of an ICS for prolonged periods of time. For example, Drake et al. described four case reports of adrenal insufficiency (presenting as hypoglycaemia) reported in children with asthma who had received high doses (500–1,500 µg/day; maximum approved dose in children under the age of 12 is 200 µg/day in most countries) of FP for 6 months or longer [21].

Growth and inhaled corticosteroids

In 1998, an FDA advisory committee reviewed the available data on growth in children following treatment with ICS and intranasal corticosteroids. The advisory committee concluded that growth suppression was a class effect that occurred with low to medium doses of cortico-steroids, even when these doses did not produce impair-ment of other measures of HPA axis function [36].

With the FDA advisory committee findings in mind, it is important to recognise that like other measures of HPA axis function, the more sensitive the growth measure, the less clinically relevant it appears to be. For example, initial knemometry studies demonstrated a significant and dose-dependent effect of ICS on lower leg growth velocity retardation [76], but these effects did not predict effects of ICS, if any, on the final height of children. The same was found to be true in year-long studies with the inhaled corticosteroid, CFC-BDP MDI [20,69]. In two separate, randomised, double-blind, placebo-controlled clinical tri-als with 200 µg CFC-BDP twice daily or placebo in school children ages 6–16 and 7–9 years, respectively, with asthma, a median growth retardation of approximately 1 cm was observed in the intervention groups relative to placebo. This small transient reduction in growth velocity

was also observed in the CAMP study, where 1,041 children from 5 to 12 years of age with mild to moderate asthma were randomised to 200 μg BUD, 8 mg nedocromil, or placebo twice daily. The children were treated for 4–6 years [64]. However, final height in adulthood among children following long-term treatment with inhaled corticosteroids appears to be comparable to that of children with asthma who were not treated with an ICS [4]. These studies indicate that low to moderate dosages of ICS are safe with respect to growth.

Bone metabolism and inhaled corticosteroids

In adults, extensive data are available on the adverse effects of ICS on bone metabolism, including osteoporosis and fractures. Inhibition of bone metabolism by ICS could have important long-term consequences, particularly in women where reductions in bone mass may ultimately result in osteoporosis and an increased incidence of bone fractures at older ages. There is, however, continuing debate as to whether a total cumulative dose or a specific daily dose range is the best predictor of bone loss.

The adverse effects of ICS on bone mineral density and bone metabolism in children with asthma are not well defined, but effects do appear to be dose related. Six months of high-dose treatment with 1,000 μg of FP in children aged 5–19 years did not result in a significant reduction in bone metabolism or bone mineral density [28]. This is in contrast with an earlier study over a period of 1 year that showed a change in bone mineral content in children aged 5–14 years treated with high doses of BDP or BUD (range of doses, 400–2,000 μg/day) [6]. Similarly, a step-down study in children aged 6–10 years who were treated with FP (1,000 μg/day) for 2 months showed a reduction in bone metabolism and lower leg growth velocity, as well as HPA axis suppression [72]. However, all adverse effects observed in the initial high-dose FP treatment period disappeared after dose reduction. It is also important to note that direct measurements on bone, as well as measures of bone biomarkers, show no evidence that low to medium doses of ICS effect bone density [5]. In this regard, the CAMP study [64], where children aged 5–12 years at study entry were treated for 4–6 years with 400 μg/day of budesonide DPI, found no evidence that long-term BUD treatment affected bone mineral density.

Adverse effects in preschool children

There is limited safety data on ICS in very young children, but the data that are available are reassuring. Lødrup Carlsen et al. showed in a randomised, multi-center, placebo-controlled, parallel group study of children ages 12–47 months, who were treated with either 100 μg of FP or placebo twice daily for 12 weeks, that FP was well tolerated, and the overall adverse event profile was similar in the two groups [46]. Urinary cortisol/creatinine ratios were slightly decreased among FP patients after 12 weeks, but there were no adverse events linked to HPA-axis suppression in this study. Another randomised, double-blind, placebo-controlled, parallel-group trial in infants aged 6–12 months receiving 0.5 or 1.0 mg of BUD as a nebulised suspension, or placebo, for 12 weeks showed that the safety profile of BUD suspension was similar to that of placebo, with no suppressive effects on adrenal function [9]. More recently, daily treatment with inhaled 250 μg FP (administered as 125 μg via a MDI with a spacer two times daily) for 18 months in children with a mean age 10 months who had recurrent wheeze and a family history of asthma was shown to have no adverse effects on the HPA axis or on linear growth [31]. However, FP treatment was associated with increases in body weight and body mass index. These results are consistent with earlier studies in 471 children aged 1–3 years who received 200 μg FP (administered as 2×50 μg via a MDI with a spacer two times daily) for 52 weeks and 40 children under 2 years of age who were randomised to either 100 μg or 250 μg of FP (adminsistered as one single puff via a MDI with a spacer two times daily) or placebo for 6 months [10,63]. Guilbert et al. conducted a clinical study in 2–3-year-old children who received FP 200 μg/day (administered as two 50-μg puffs via an MDI with a spacer two times daily) or placebo for 2 years and showed that there was a mean difference of −1.1 cm from placebo in height at the end of the 2-year treatment period [21]. In this same study, a −0.7 cm difference in height from placebo was observed 1 year following the cessation of study medication [29]. The authors questioned, however, whether height would have become similar in the two groups as the cohort matured. Finally, in the IFWIN study, children aged 0.5–4.9 years were randomised to receive 200 μg FP (administered as 100 μg via a MDI with a spacer twice daily) or placebo [52]. After 6 months, the FP group had a decrease in Z-score (the height standard deviation scores calculated from the UK 1990 reference curves). [26,78] At 5 years of age, both the FP and the placebo groups had similar changes in Z-scores relative to the pre-treatment Z-scores. All FP-treated children had received treatment for at least 9 months. The temporary reduction in growth in the FP group is comparable to the effects observed in school children with asthma. Together, these data show that with respect to growth, ICS are well tolerated and have minimal or no long-term effects on growth when used in appropriate doses.

Conclusions

Inhaled corticosteroids remain the most effective anti-inflammatory therapy for the treatment of adults and school-aged children with asthma. The efficacy of ICS in preschool children with episodic viral wheeze remains controversial, while ICS treatment of preschool children with multiple-trigger wheeze appears to be at least somewhat effective. However, the effect size in preschool children with multiple-trigger wheeze is smaller than the effect size in school-aged children with asthma.

In school children with asthma, small-particle ICSs, such as ultrafine HFA-BDP and ciclesonide, are as effective as fluticasone propionate on a microgram for microgram basis, and at least as effective, at half the dose, as BUD and CFC-BDP. The small particle ICSs appear to have theoretically a very favourable benefit/risk ratio in preschool children, but prospective clinical studies with these ICS in this age group are needed. ICS are generally well tolerated in both school-aged and preschool children, and adverse events tend to be minimal in both age groups when the ICS is used in appropriate doses.

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