ABSTRACT. In the treatment of childhood asthma, balancing safety and efficacy is key to achieving optimal therapeutic benefit. Inhaled corticosteroids (ICS), because of their efficacy, remain a cornerstone in managing persistent pediatric asthma, but also are associated with significant adverse effects, including growth suppression. Consequently, careful attention must be given to balancing their safety and efficacy, which should include an understanding of airway patency and systemic absorption (dose, disease severity, propellant and lipophilicity of inhalant), bioavailability (inhala
tion technique, propellant, delivery devices, and hepatic first-pass metabolism), techniques for using minimum effective doses (dosing time, add-on therapy), and reduction of other exacerbating conditions (allergens, influenza, upper-respiratory diseases). The growth-suppressive effects of ICS may be most evident in children with: 1) mild asthma because the relatively high airway patency may facilitate increased levels of deposition and steroid absorption in more distal airways, and 2) evening dosing that may reduce nocturnal growth hormone activity. A step-down approach targeting a minimum effective dose and once-daily morning dosing is suggested for achieving the most acceptable safety/efficacy balance with ICS. The achievement of regular, safe, and correct ICS use requires significant knowledge and time for both caregiver and patient. Chromones, methylxanthines, long-acting β-agonists, and leukotriene receptor antagonists are currently available alternatives to ICS for the control of persistent childhood asthma. Chromones are safe but, like methylxanthines, are difficult to use and frequently result in compromised effectiveness. Long-acting β-agonists are not recommended as monotherapy for persistent asthma. Several factors that support leukotriene receptor antagonists as a therapeutic option for mild-to-moderate persistent pediatric asthma include established efficacy, good safety profiles, and simple, oral dosing. Physicians must evaluate and compare the balance of safety and efficacy for each agent to determine the appropriate asthma therapy for individual patients. Pediatrics 2002; 109:381–392; pediatric asthma, inhaled corticosteroids, airway deposition, bioavailability, leukotriene receptor antagonists.

Abbreviations. ICS, inhaled corticosteroids; GI, gastrointestinal; CS, corticosteroids; BDP, beclomethasone dipropionate; pMDI, pressurized metered-dose inhaler; CFC, chlorofluorocarbon; DPI, dry powder inhalers; HFA, hydrofluoroalkane; FEV1, forced expiratory volume in 1 second; CAMP, Childhood Asthma Management Program; PEFR, peak expiratory flow rate.

For most children, the onset of asthma occurs before the age of 2 years, underscoring the need for early treatment not only to control the debilitating effects of asthma symptomatology but also to prevent irreversible structural changes that can lead to permanent airway obstruction. Because asthma requires chronic—often lifelong—treatment, a critical issue in the management of pediatric asthma is balancing the safety and efficacy of asthma interventions to achieve optimal long-term results. This review will examine some of the challenges to balancing safety and efficacy associated with inhaled corticosteroid (ICS) therapy and explore the potential benefits of other available alternative therapies for managing persistent mild-to-moderate pediatric asthma.

ICS
As the gold standard for the long-term management of asthma in adults and children, ICS reduce both asthma symptomatology and the markers of airway inflammation. Early intervention with ICS may preserve pulmonary function and prevent irreversible airway obstruction, remodeling, and hyperresponsiveness. Nevertheless, important challenges present themselves with the use of ICS in young children, particularly with the potential for systemic adverse effects, including growth suppression.

Sources and Determinants of Systemic Bioavailability of ICS
Although ICS were developed to replace efficacious, but more highly bioavailable oral glucocorticosteroids, they can nonetheless manifest detectable systemic bioavailability. ICS can be absorbed from both the gastrointestinal (GI) system and the airway mucosa. Thus, factors that increase the degree of airway delivery generally increase the systemic bioavailability of a drug. If sufficient drug enters the blood, effects can be detected using sensitive assays of the hypothalamic-pituitary axis or methods to measure childhood growth.

Individual ICS and Delivery Devices
Systemic bioavailability of ICS occurs either through the inhaled fraction of corticosteroids (CS) that makes it into the airways (~20%) or by swallowing ~80% of the delivered CS that makes it no further into the airway than the back of the throat. The swallowed CS is subject to hepatic first-pass inactivation after it is absorbed from the gut. For fluticasone and mometasone, approximately 99% is...
inactivated in the liver, and for budesonide and triamcinolone, 90% and 80% to 90%, respectively, are inactivated. Beclomethasone dipropionate (BDP), however, is not entirely inactivated in the hepatic first pass (60% to 70%), and an active metabolite (beclomethasone-17-monopropionate) is formed that has a potency similar to the parent BDP. It would therefore appear that the newer ICS (fluticasone and mometasone) have a superior safety profile based on hepatic inactivation of noninhaled drug and that they should generate less concern about minimizing the swallowed portion of the drug.

Once present in the systemic circulation, the degree of lipophilicity of each ICS may also have an important influence. Fluticasone and mometasone are highly lipophilic drugs and therefore are more easily distributed into the systemic tissue compartments. Consequently, they have a large volume of distribution at steady state. In contrast, triamcinolone and budesonide have lower lipophilicity and, consequently, a smaller volume of distribution. Because the systemic tissue storage of an ICS acts as a slow release reservoir, the drugs with higher lipophilicity would take a longer time to be cleared from the larger distribution volume. Their lipophilicity could thus increase the potential for producing systemic adverse effects. The risk may be offset by the general approach to use relatively lower μg doses of the more lipophilic and thus more potent ICS.

The majority of drug in the blood, however, originates from that deposited in the lower airways, where it is directly absorbed into the vasculature without undergoing metabolism or inactivation. Therefore, minimizing GI bioavailability via the selection of newer ICS will not necessarily eliminate the possibility of systemic bioavailability, and the risk of systemic adverse effects, such as growth suppression, and a dose-related growth suppression could be expected of both newer and older ICS. Likewise, factors that increase airway dose and delivery (ie, milder disease, increasing the μg dose, use of spacers, formulation changes that result in smaller particle sizes, improved inhalation technique) may provide better benefit but may also increase the systemic bioavailability of the drug and thus increase the risk of systemic adverse effects. For example, spacers improve airway delivery and are routinely recommended, but they do demonstrate variability in delivery across devices and simultaneously enhance systemic bioavailability, thus raising concerns about systemic adverse effects as well. Fortunately, most patients can be managed by delivering relatively low ICS doses to the airways.

Formulation

Current pressurized metered-dose inhaler (pMDI) formulations of ICS, which use chlorofluorocarbon (CFC) as the propellant, are being reformulated to dry powder inhalers (DPIs) or pMDIs with alternative propellants (eg, hydrofluoroalkane [HFA]). The change is mandatory because of the possible contribution of CFC to depletion of the earth’s ozone layer. Each new formulation of an older drug has unique airway and GI delivery characteristics and thus unique safety and efficacy profiles. For example, the older pMDI formulation of budesonide delivered much less drug to the airways than the newer Turbuhaler DPI formulation (AstraZeneca, Södertälje, Sweden). Likewise, the change in formulation of the vehicle propellant from CFC to HFA may increase the bioavailability of ICS by improving the airway delivery, thereby increasing the potential for systemic adverse effects. The HFA formulation of BDP delivers smaller-sized particles (the average particle size of HFA-BDP is 1.1 μm compared with 3.5 μm for CFC-BDP). Furthermore, HFA-BDP’s average spray force is softer (3 times less), and has a longer duration and a warmer temperature, than that of CFC (the temperature is approximately +5°C for HFA-BDP vs −20°C for CFC-BDP). Consequently, there is more lung deposition and less mouth deposition for HFA-BDP than for CFC-BDP. In a clinical trial, the dose-response (forced expiratory volume in 1 second [FEV1], % predicted) curve for HFA-BDP was shifted to the left compared with the dose-response curve for CFC-BDP. To achieve the same improved FEV1 as HFA-BDP, 2.6 times the dose of CFC-BDP would be required. With an increased airway delivery, there may be increased absorption and increased risk of systemic adverse effects. In contrast, HFA formulations of other drugs may deliver lower amounts to the airway compared with the older CFC formulation.

In a separate pharmacokinetic comparison, the HFA formulation produced a significantly increased maximum concentration of drug (Cmax) and area under the curve (AUC) (P < .001 and P < .005, respectively) compared with the CFC formulation, resulting in up to twofold greater absorption of BDP. Therefore, clinically important systemic adverse effects may be expected with the HFA if a nominal 1:1 dose switch were made between CFC and HFA formulations of BDP.

Disease Severity

In children with mild asthma, airways are more patent than in those with more severe asthma; consequently, drug deposition and absorption may be higher. The resulting increase in steroid absorption could enhance all the clinical effects of ICS—including adverse effects—and possibly lead to growth suppression.

Limited evidence for this explanation has been gleaned from studies using β-agonists and ICS. Radioactively labeled inhaled salbutamol has been shown to accumulate much more readily in the peripheral lungs of normal persons than in persons with asthma. Furthermore, this difference was consistent, regardless of the delivery device used. In addition, a twofold increase in FEV1 was associated with a 1.5-fold increase in drug deposition, suggesting that the degree of airway patency is directly correlated with peripheral drug deposition. Additionally, when fenoterol was administered by an MDI at a fixed dose (4 mg) to either normal or asthmatic individuals, fenoterol absorption, as measured by the maximum concentration of drug (Cmax), was substantially higher in normal persons (3.1 ng/
mL) than in asthmatic individuals (1.6 ng/mL).\textsuperscript{20,21} Concomitantly, the heart rate increased by 45 beats per minute in the normal individuals but only 30 beats per minute in asthmatic individuals.

The pharmacokinetics of inhaled fluticasone (1000 μg) have been measured in normal healthy (FEV\textsubscript{1} = 108% predicted) and asthmatic individuals (FEV\textsubscript{1} = 54% predicted).\textsuperscript{22} As shown in the mean plasma concentration versus time curve (Fig 1), the AUC in healthy controls was greater (2815 pg/mL/h) than in asthma patients (1082 pg/mL/h). Similarly, the mean peak plasma concentration, $C_{\text{max}}$, was greater (383 pg/mL) in healthy controls than in asthmatic patients (117 pg/mL). Of note, systemic availability mildly correlated with baseline FEV\textsubscript{1} ($r = 0.47; P = .02$).

By extension, these data may suggest that, for persons with mild asthma, or for those with the greatest airway patency, drug deposition and absorption would be substantially greater than in those patients who have more severe asthma or the least airway patency. Such elevated availability of an ICS in the more patent airways of a person with mild asthma could account for the ICS budesonide-associated growth suppression seen in children with mild asthma (see below). Although support for this explanation can be gleaned from studies using both β\textsubscript{2}-agonists and ICS, potential flaws include a lack of direct extrapolation of results from a nonasthma to asthma comparison to a comparison across severity levels within an asthmatic population.

GROWTH SUPPRESSION

Although ICS have been proven highly efficacious for the treatment of childhood asthma, concerns over adverse effects on children’s growth have caused the Food and Drug Administration to issue new guidelines for the labeling of CS, both inhaled and intranasal.\textsuperscript{10} A recent survey indicated that although 71% of the respiratory specialists such as allergists and pulmonologists believe that clinically important growth suppression can be induced by ICS, almost 84% of these specialists reported, however, that they have rarely or never seen growth suppression in their pediatric patients treated with ICS. The risk for growth suppression with ICS nevertheless remains a real one for some children. Many factors likely influence this risk including total dose, drug delivery device and technique, genetic predisposition, age, adherence, and asthma severity.

Influence of Asthma Severity on ICS-Induced Growth Suppression

Three separate but related long-term trials—designated A, B, and C—compared the growth-suppressing effects of budesonide nebulizing suspension with conventional asthma therapy in young children 6 months to 8 years of age (Fig 2).\textsuperscript{4} These trials included a 12-week, randomized, double-blind phase followed by a 52-week, open-label extension during which growth was monitored. In study A, persistent asthma severity was classified as mild persistent, and patients in this group received no ICS before randomization. Moderate-to-severe persistent asthmatic patients were included in study B, and they had received ICS before randomization with additional ICS postrandomization only as needed. Mild-to-moderate persistent asthmatic patients included in study C varied in whether they had received ICS before randomization, and additional ICS therapy was administered only as needed after randomization. Conventional asthma therapy included any available therapy including ICS in studies B and C. No significant differences in growth velocity were detected between the budesonide and conventional treatment groups in studies B and C. In study A, however, which included ICS-naïve children with the mildest degree of asthma, budesonide treatment significantly suppressed growth by 0.8 cm per year. These studies show that, in children with more severe asthma and previous exposure to ICS, there is no difference in growth velocity between those treated with budesonide and those treated with conventional asthma therapies. This contrasts with the result in milder asthma and may result, in the more severe patients, from a lower degree of airway patency and deposition, and thus less systemic bioavailability.

Fig 1. Plasma fluticasone concentration for 12 hours after inhalation. In healthy volunteer controls (open triangles), a 1000-μg inhalation of fluticasone produced a mean plasma concentration versus time curve that was significantly greater than inhalation of the same quantity of fluticasone in asthmatic patients (filled circles). Such elevated availability of an ICS in more patent airways could account for ICS-associated growth suppression in children with mild asthma. Adapted from Brutsche et al.\textsuperscript{22}
Long-Term Studies

The effect of ICS on linear growth was examined in mild-to-moderate asthmatic children 5 to 12 years of age in the Childhood Asthma Management Program (CAMP).23 Children were randomly assigned to receive budesonide, nedocromil, or placebo twice daily for 4 to 6 years. The budesonide group demonstrated a clear decrease in growth velocity during the first year that resulted in a mean height increase that was 1.1 cm less than the mean increase in the placebo group (22.7 vs 23.8 cm; \( P = .005 \)). The decreased growth velocity did not continue beyond the first year and by the end of the study, the growth velocity was similar for all groups. The 1.1 cm between-group difference was still present at the end of the study, however, indicating a lack of catch-up growth during this period (Fig 3).

Nevertheless, a separate study suggested that children treated with ICS still reach their target adult height.24 Children treated with budesonide for an average of 9.2 years appeared to reach their calculated target adult height, based on parental height, compared with 18 control patients with asthma who had never been treated with ICS and also with 51 healthy siblings not on asthma therapy. The results of this study are difficult to interpret, however. First, the control group decreased from 62 to 18 participants, mainly owing to patients requiring inhaled or oral CS treatment. In addition, this study was not powered to be able to distinguish a 1.1 cm loss of height as measured in the CAMP because the equation used to compute the target adult height had a large variance (a 95% confidence interval of approximately \( \pm 10 \) cm).25 If the 1.1-cm difference occurred, it more than likely would not be detectable.

**STRATEGIES FOR BALANCING SAFETY AND EFFICACY WITH ICS**

Balancing the unquestionably beneficial actions of ICS against their risk for systemic adverse effects, including growth suppression can be challenging, especially in young children. A summary list of these strategies is presented in Table 1.

One strategy for achieving a satisfactory benefit/risk balance in moderate-to-severe asthma may be a step-down approach to ICS therapy: Start at a high dose to gain control of asthma-related inflammation and then gradually reduce to the minimum effective dose, which would be continued to maintain long-term control. Optimally, obtaining a minimum effective dose could depend on:

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**Fig 2.** Three pivotal studies from the United States: mean growth velocity. In children with more severe asthma and previous exposure to ICS, there is no significant difference in growth velocity between those treated with budesonide (filled column) and conventional asthma therapies (unfilled column) by the end of the 1-year open-label phase. –ICS indicates no prerandomization use of ICS; +ICS, prerandomization use of ICS; ±ICS, prerandomization use of ICS or bronchodilator therapy. *\( P = .002 \) budesonide therapy versus conventional asthma therapy. Adapted from Skoner et al.4

**Fig 3.** Reduction of growth velocity occurs within the first year of budesonide use. Results from CAMP. Left panel: at the end of the treatment period, the mean increase in height in the budesonide group was 1.1 cm less than the mean increase in the placebo group (22.7 vs 23.8 cm; \( P = .005 \)). The mean height increase was similar in the nedocromil and placebo groups (\( P = .65 \)). Right panel: the difference between the budesonide and placebo groups in the rate of growth was evident primarily within the first year of treatment and did not increase later. All groups had similar growth velocity by the end of the treatment period. Adapted from CAMP.23
TABLE 1. Techniques for Balancing Efficacy and Safety of ICS in Children

1. Selection and use of ICS
   - Select safest ICS drug
   - Use minimum effective dose
   - Dose in morning when once-daily dosing
   - If control is poor, add another controller rather than double dose of ICS
   - To maximize ICS delivery to lungs, consider:
     a. CFC versus HFA propellant formulation
     b. pMDI versus DPI formulation
     c. Use of a spacer device
     d. Patient technique
   - Rinse mouth of ICS and discard
2. Use ICS-sparing strategies
   - Reduce allergens and smoke
   - Insulate with influenza vaccine
   - Diagnose and treat rhinosinusitis or gastroesophageal reflux disease
   - Use add-on therapies
3. Monitor growth at all ICS doses
4. Monitor eyes* and bone mineral density when using ≥1600 µg/day ICS†
5. Consider first line alternatives to ICS for mild persistent asthma

* Cataracts/glaucoma; † BDP equivalent.

1. Rigorous smoke and allergen environmental controls (reduce airway inflammation);
2. Vaccination for influenza (prevent a flu-induced exacerbation);
3. Diagnosis and treatment of concomitant conditions that could worsen asthma (ie, rhinitis, sinusitis, gastroesophageal reflux disease); and
4. Appropriate use of add-on therapy.

As long as a minimum effective dose is ensured during thoughtful, purposeful, and regularly scheduled assessments, clinicians and parents alike may be willing to accept the risk of growth suppression if the clinical benefits are sufficiently explained and adequate, and then subsequently realized. In actual clinical practice, the appropriateness of a step-down dose usually is based on maintaining improvements in symptomatology and pulmonary function, but unfortunately, inflammation control cannot be used as an additional guide at this time.

The time of day when the ICS are administered—morning or evening—appears to influence the risk for growth suppression. A 4-week study that included children 5 to 12 years of age with moderate intermittent asthma examined the growth suppressing effects of budesonide (800 µg) given as a single dose in the morning or as 2 divided doses—400 µg in the morning and 400 µg in the evening. Growth rates were significantly lower in children receiving an evening dose [0.27 ± 0.04 mm/wk] than in children receiving only a morning dose [0.38 ± 0.05 mm/wk].26 Indeed, evening exposure is one possible explanation for the differential effects on growth of intranasal beclomethasone (bid, growth suppression) and intranasal mometasone (qd, no growth suppression) in children with allergic rhinitis.27,28 Together, these findings indicate that morning dosing, in conjunction with downward dose titration, are methods that can be used to mitigate the growth suppressing actions of ICS while maintaining efficacy in pediatric asthma.

Frequently, when an asthmatic child is insufficiently controlled on an appropriate ICS dose, a decision must be made about whether to double the ICS dose or simply add on a second nonsteroidal controller medication. Support for the latter is gleaned from a study showing that, in children treated with ICS, halving the ICS dose and adding a second nonsteroidal drug was associated with faster short-term growth with no loss of asthma control, versus maintaining the original higher ICS dose alone.29 The results of these safety studies support the widely-held recommendations to use the lowest effective dose, to dose once-daily in the morning if possible, and, in poorly controlled adherent patients, to add on non-ICS therapy rather than to double the ICS dose. In other words, when concerned about an ICS dose, consider nonsteroidal add-on therapy to assist in ICS dose reduction.

Safety management includes monitoring the patient’s growth every 3 to 6 months and interpreting the resultant measurement and changes. Rinsing the mouth after administration to minimize the swallowed portion even with spacer use (with pMDI to reduce oropharyngeal deposition) is recommended. Furthermore, attention should be given to potency when considering µg dosing of a newer, more potent ICS that replaces a less potent, older ICS. For example, a clinically equivalent dose of fluticasone and BDP may be different by twofold (eg, about half the µg dose of BDP for fluticasone).

When the use of ICS raises concerns about safety, alternative therapies can be used. As previously discussed, this may be especially important in children with the mildest asthma, in whom growth impairment can result from ICS, but probably not from the disease itself. This contrasts with moderate-to-severe asthma, where growth impairment may result from the disease, but probably not from ICS.

The following sections review alternative therapies as well as add-on therapies that can reduce the amount of ICS needed to maintain control. Physicians must evaluate the balance of safety and efficacy for each agent to determine the appropriate therapy for individual patients.

CHROMONES

Cromolyn has been available for use for over 30 years as an inhaled antiinflammatory therapy for persistent asthma. Although its exact mechanism of action is not known, it is thought to stop the antigen-induced release of mediators of inflammation from mast cells.30 Cromolyn’s efficacy has been demonstrated in adults,31–34 and used in patients as young as 2 years of age using a nebulizer. Although patients taking cromolyn have experienced minor adverse effects such as cough after inhalation and eczema in the mouth area, no serious adverse effects have been noted.35

Clinical trials in young children have shown that cromolyn is safe and efficacious as either monotherapy36–40,41 or in combination with β2-agonists.3

In an earlier 10-week clinical trial, the diary scores of asthmatic children aged 8 years and older showed significant improvement of overall asthma severity.
and breathlessness ($P < .05$) and pulmonary function (peak expiratory flow rate [PEFR] and percent predicted FEV$_1$ at final visit [$P = .04$] compared with placebo). Cromolyn, therefore, was often recommended as first-line therapy in school-aged and preschool-aged children having mild-to-moderate persistent asthma.

This recommendation has been challenged, however, especially for the preschool population. A randomized trial in over 200 children 1 to 4 years of age with moderate asthma showed that cromolyn was no more effective than placebo in this age group. Patients received either cromolyn (10 mg tid) or placebo for 5 months using inhalers with spacer devices and face masks. The results showed there were no significant differences in the percent of symptom-free days, number of symptoms per day, or use of rescue medication. Such data support the recommendation that cromolyn should not be used as first-line preventive therapy in this young patient population.

Cromolyn added to ICS therapy has shown little or no benefit, suggesting it is not an effective steroid-sparing therapy, and current pediatric guidelines do not recommend its use as add-on therapy. Although cromolyn has been shown to be safe for pediatric use, its placebo-like efficacy as prophylactic therapy in children with mild-to-moderate persistent asthma and its 3 to 4 times daily dosing requirement, together with using a spacer or nebulizer, have contributed to its decreased use. The strength of cromolyn therapy is its safety; its weakness is in its efficacy.

**Nedocromil sodium**, an inhaled therapy also belonging to the chromone class, blocks the release of mediators from mast cells. It also appears to inhibit the action of eosinophils and their release of mediators. It has proven to be efficacious in adults with mild-to-moderate asthma and is indicated for children with mild-to-moderate asthma as young as 6 years of age.

In children, nedocromil has been shown to improve symptoms and pulmonary function and to reduce the need for rescue bronchodilator use, although its effect on pulmonary function has been questioned. In the CAMP study, nedocromil significantly reduced the number of urgent care visits ($P = .02$) and courses of prednisone ($P = .01$), but was similar to placebo in all other endpoints, including airway hyperresponsiveness, prebronchodilator and postbronchodilator FEV$_1$, rate of hospitalization, daily symptom score, and rescue bronchodilator use.

Added to ICS therapy, nedocromil appears to be moderately beneficial in asthmatic adults, but this efficacy has not been demonstrated in children. Pediatric asthma guidelines indicate nedocromil should not be used as add-on therapy, at least until additional studies can prove it is beneficial. Nedocromil’s safety profile is similar to that of placebo. Serious adverse effects have not been reported, but patients have complained about nedocromil’s unpleasant taste. Similar to cromolyn, nedocromil’s questionable effect on pulmonary function and bid–tid dosing requirement suggest that other antiinflammatory therapies may be preferable in treating mild-to-moderate asthma. Like cromolyn, the strength of nedocromil is its safety; its weakness is its efficacy.

**METHYLXANTHINES**

Although theophylline has been used to treat asthma for over 60 years, its complete mechanism of action is still unclear. As a phosphodiesterase inhibitor, it relaxes airway smooth muscle (bronchodilation) and consequently improves airway function.

In children, theophylline is effective in treating mild-to-moderate asthma. In a year-long study in 195 children aged 6 to 16 years of age with mild-to-moderate asthma, theophylline (target blood level between 8 and 15 µg/mL) or BDP (84 µg qid) effectively improved pulmonary function (FEV$_1$ [Fig 4] and PEFR), methacholine hypersensitivity, hospital visits/physician visits, days out of school, and overall physicians’ global evaluation. The patients on beclomethasone, however, required less β$_2$-agonist use and fewer systemic CS rescues (18.6% vs 36.6%...
for beclomethasone and theophylline, respectively; \( P = .007 \).

Steroid-dependent asthmatic children demonstrated the added benefit of combining theophylline with ICS therapy. Patients taking theophylline showed significant improvement in daily PEFR (\( P < .01 \)), percent symptom-free days (\( P < .01 \)), \( \beta_2 \)-agonist use (\( P < .01 \)), and additional CS therapy (\( P = .02 \)) compared with placebo.\(^{59} \) These data support the recommendation that theophylline can be used as add-on therapy to antiinflammatory medications such as ICS, and although it can be considered an alternative first-line therapy, it is not preferred for persistent asthma.\(^{42} \)

In children, theophylline has been linked to changes in behavior and school performance.\(^{38, 60} \) These adverse effects are more common when blood levels surpass the therapeutic range (10 mg/L–20 mg/L in adults, 5 mg/L–15 mg/L in children), but are also seen at therapeutic concentrations. Adverse effects such as headache and other effects on the central nervous system, tremor, nausea, vomiting, and gastric irritation have been reported more frequently in patients taking theophylline.\(^{61} \)

In addition to its safety profile, the need for optimal dose determination and plasma concentration monitoring have contributed to theophylline’s decline in popularity, despite its low cost. Theophylline is metabolized by the cytochrome P450 isoenzymes in the liver, which raises the possibility of interactions with other drugs metabolized by these complexes. For this reason, it is important to monitor blood levels and clearance in patients receiving theophylline once the physician has determined the best dose. Consequently, although theophylline has proven to be efficacious in the treatment of adults and children with mild-to-moderate asthma, these considerations may make other treatment options more desirable.

LEUKOTRIENE RECEPTOR ANTAGONISTS (LTRAs)

Because they can reduce the airway inflammation, bronchial hyperactivity, and smooth muscle contraction associated with asthma,\(^{62, 63, 64} \) LTRAs may be a suitable alternative to ICS in some patients or reduce the need for ICS in others. Pediatric asthma guidelines state that LTRAs may be an alternative to low-dose ICS therapy in mild persistent asthma and may be an effective add-on to ICS therapy in moderate persistent asthma.\(^{42} \) Indeed, a recent controlled study concluded that, in ICS-treated children with persistent asthma, the addition of montelukast 5 mg provided significant improvement in pulmonary function and in symptoms, despite significant reduction in \( \beta_2 \)-agonist use.\(^{65} \)

Zafirlukast

Zafirlukast, the first LTRA approved in the United States, has demonstrated effectiveness in the management of mild-to-moderate asthma in clinical trials by improving pulmonary function and by reducing the clinical symptoms of asthma as well as the need for ICS.\(^{66} \) Zafirlukast is indicated as twice-daily oral treatment for the management of asthma in children as young as 7 years of age. Because it is an inhibitor of the CYP450 isoenzyme CYP3A4, however, it can increase concentrations of certain concomitant medications, including theophylline.\(^{67} \) Its use, therefore, requires close monitoring of plasma drug levels when concomitantly prescribed. In addition to potential drug interactions, food reduces zafirlukast’s bioavailability, and it should be taken 1 hour before or 2 hours after a meal.\(^{68} \)

Montelukast

Clinical studies have shown that montelukast, the most recently approved LTRA, is also effective in the management of pediatric asthma. As once-daily oral therapy, montelukast is indicated for the treatment of mild-to-moderate asthma in adults and children as young as 2 years of age. In an 8-week study, montelukast administered once daily was compared with placebo in asthmatic children as young as 6 years of age.\(^{69} \) Almost 40% of the children were receiving concomitant ICS therapy during the trial. At baseline, the mean FEV\(_1\) was 72% of normal, and on average, the children required 3.3 \( \beta \)-agonist puffs daily—reflecting at least mild-to-moderate persistent asthma. Significant improvements in FEV\(_1\) were noted for the montelukast group over the course of the study (Fig 5), accompanied by an immediate decline in \( \beta \)-agonist use beginning on the first day of use (Fig 6). Furthermore, montelukast provided the same positive effects on pulmonary function whether the patients were receiving ICS or not.\(^{70} \)

In children 2 to 5 years of age, montelukast’s 4-mg chewable tablet efficacy was evaluated during a 12-week multinational study. Compared with placebo, montelukast significantly improved \( \beta \)-agonist use (\( P = .001 \)), daytime asthma symptom score (\( P = .003 \)), days with symptoms (\( P = .02 \)), days without asthma (\( P = .002 \)), CS rescues (\( P = .008 \)), physician’s global evaluation (\( P = .007 \)), and peripheral blood eosinophils (\( P = .034 \)). Therefore, montelukast improved asthma control significantly in patients aged 2 to 5 years with asthma.\(^{71, 72} \)

The safety profile of montelukast is similar to that of placebo\(^{33, 69, 72} \) and there are no known drug interactions, which precludes the need for plasma monitoring. Furthermore, because montelukast is available for children as young as 2 years of age, a safety study was undertaken in 2- to 5-year-old patients with asthma who received montelukast (4-mg chewable tablet) for 12 weeks. The adverse experience profile of montelukast was comparable to placebo for all parameters examined (asthma, fever, upper respiratory infection, frequency of discontinuation attributable to clinical adverse experiences, and the frequency of individual laboratory adverse experiences).\(^{72} \) Its bioavailability is not affected by food, so it can be taken at any time, regardless of mealtime. Because montelukast is available as a chewable tablet (5 mg for children 6–14 years of age and 4 mg for children 2–5 years of age), its administration is simple and convenient for children.\(^{73} \)
LONG-ACTING $\beta_2$-AGONISTS

Salmeterol, a long-acting $\beta_2$-agonist, is indicated for long-term use and is available as both an aerosol and an inhaled dry powder, the latter of which is approved for children as young as 4 years of age. Both formulations of salmeterol are more efficacious than short-acting $\beta_2$-agonists and placebo in treating mild-to-moderate asthmatic children, with significant bronchodilation lasting up to 12 hours.

In a 12-week, randomized, double-blind study in children 4 to 11 years of age with moderate persistent asthma, patients receiving salmeterol (50 $\mu$g bid) had a significantly higher FEV$_1$ at all time points up to 12 hours postdose for 12 weeks compared with patients on placebo (week 12: $P \leq .005$). Significant improvements over placebo in mean percent of predicted PEFR ($P = .008$) and patient-measured PEFR (morning: $P < .001$; evening: $P = .010$) were also observed for the duration of the study in patients taking salmeterol. Rescue use of the short-acting $\beta_2$-agonist decreased significantly in the salmeterol group ($-0.8 \pm 0.2$ puffs/day vs $-0.3 \pm 0.1$ puffs/day for salmeterol and placebo, respectively; $P = .004$), but there was no significant change in nights without awakenings.

Longer trials examining the effect of salmeterol in children with mild-to-moderate asthma have produced mixed results. In a 1-year randomized, double-blind trial, in children 6 to 14 years of age, salmeterol did not significantly improve airway hyperresponsiveness compared with placebo, but it did significantly increase pulmonary function (FEV$_1$, morning and evening PEFR). In another year-long, randomized, double-blind parallel study in mild-to-moderate asthmatic children 6 to 16 years of age, however, children taking salmeterol (50 $\mu$g bid) did not experience a significant improvement of FEV$_1$ during the study or an improved airway hyperresponsiveness. At the end of the study, the PD$_{20}$ declined by a $-0.73$ doubling dose ($P = .05$).

The reason for the decreased FEV$_1$ and the increased airway hyperresponsiveness in salmeterol-treated patients was not determined, but there are two possible explanations. First, tolerance may have developed to salmeterol’s bronchoprotection as it has been shown to lead to decreased bronchoprotection against methacholine challenge and exercise-induced bronchoconstriction. The reduction in FEV$_1$ did not appear to be prevented in mild-to-moderate asthma patients on ICS therapy. Although salme-
trol has a protective effect against exercise-induced asthma, the duration of this effect may wane even during regular once-daily salmeterol treatment despite the reduced frequency of dosing and despite concomitant use of ICS in children. Similarly, regular treatment with long-acting β₂-agonists may decrease the effectiveness of short-acting β₂-agonists in protecting against bronchoconstriction. Another possible reason for the decrease in FEV₁ could be unchecked airway inflammation. Because long-acting β₂-agonists have not been shown to have in vivo antiinflammatory actions, their bronchodilating and symptom-relieving benefits could potentially mask continuing airway inflammation and, consequently, worsening asthma over time. Unhindered inflammation could also explain the greater number of asthma exacerbations that required oral CS courses in the salmeterol-treated patients as compared with ICS-treated patients (17 vs 2, respectively).

Current pediatric guidelines state that long-acting β₂-agonists should not replace antiinflammatory therapy but should be considered as add-on therapy. In children with moderate-to-severe asthma, combining salmeterol with budesonide improved morning PEFR (P < .001), evening PEFR (significant during first 4 weeks of treatment; P = .014), symptom-free days (P < .05), and reduced the use of rescue medications (during the last 8 weeks; P < .05).

Salmeterol has a safety profile comparable with placebo. As an inhaled therapy, adherence to salmeterol may be adversely affected by its method of administration.

**ADHERENCE ISSUES IN PEDIATRIC ASTHMA**

The efficacy of an asthma intervention, as evaluated in controlled clinical trials, is actually a measure of whether a particular drug can work, not necessarily whether it will work in clinical practice. Actual drug effectiveness, which reflects whether it will produce its intended effect in the clinical setting, is influenced by real world variables, the most important of which may be patient adherence. Adherence may be especially difficult to gain in the mildest patients, who clinically have the least disease burden.

In controlled clinical trials, doses are often fixed, patient adherence is carefully monitored, and the patients typically receive more extensive asthma education. In other words, the environment is much more controlled relative to the everyday clinical practice setting where dosing varies widely, patient education about asthma is often poor, and, most importantly, patient adherence can vary considerably.

In the clinical setting, patient adherence to the prescribed asthma regimen is influenced by numerous factors including mode of administration, dosing frequency, onset of action, perceived efficacy, and anticipated adverse effects. The importance of adherence to and proper use of ICS has been demonstrated in a study that showed a significant inverse relationship between asthma hospitalization rates and the ratio of ICS to β₂-agonist use. A Canadian survey of 603 asthmatic adults revealed that approximately half the patients held unfounded fears and misconceptions about the adverse effects and efficacy of ICS, and they expressed misgivings about taking these agents regularly. In addition, 75% of these patients admitted that they had not discussed their concerns with their physicians. Such steroid-phobia could understandably lead to decreased adherence to prescribed therapy and, subsequently, diminished therapeutic effectiveness.

Adherence rates have also been shown to be significantly lower with inhaled asthma medication than with oral formulations. This raises the possibility that one reason we may not see much ICS-induced growth suppression in children in a clinical practice setting is that they are self-titrating downward through poor adherence. Obviously, poor adherence is not a solution to the possibility of growth suppression but, rather, part of the challenge in balancing risks and benefits because it also leads to poor disease control, overutilization of health care resources, and unabated airway remodeling.

High adherence rates, in contrast, may enhance the effectiveness of an asthma therapy. In a drug preference study that included asthmatic children 6 to 14 years of age, the acceptability of once-daily montelukast was compared with inhaled cromolyn 4 times daily over a 4-week period. Over 80% of the children, as well as their caregivers, preferred once-daily treatment with oral montelukast (P < .001). Additionally, significant differences were observed between groups in the rates of adherence, with 78% of the montelukast-treated children adhering on more than 95% of the treatment days compared with 42% of the cromolyn-treated children (P < .001). The number of study discontinuations caused by asthma exacerbations was markedly fewer in the montelukast group than in the cromolyn group as well (P < .07). These results suggest that oral therapies such as montelukast may encourage adherence in the management of pediatric asthma, at least when compared with an inhaled asthma medication.

Patient satisfaction with medication may also play an important role in the effectiveness of asthma therapy. In a survey of over 5000 asthma patients, those who did not feel confident about the efficacy of the medication or their ability to take their medications as directed were 8 times more likely to be dissatisfied with their treatment. These patients may require counseling on the proper use of inhalers or nebulizers to increase confidence and thereby improve adherence and treatment outcomes.

**CONCLUSION**

Balancing safety and efficacy issues is an ongoing challenge in the treatment of pediatric asthma. ICS continue to be a mainstay in the control of persistent asthma because of their clear efficacy. Of all the therapies available for treatment, however, ICS require the most attention to maintain the balance between safety and efficacy. Children with mild asthma may be most susceptible to the growth-suppressing action of ICS, ostensibly because more of their distal airways are exposed to the ICS, and more drug is absorbed there. This raises the question: Will
the risk for growth suppression among children with moderate or severe asthma increase as airway patency and, thus, drug deposition/exposure increase in response to ongoing ICS therapy? The answer is elusive and complicated by the fact that adherence may decrease over time with ICS therapy, reducing not only the beneficial actions of these agents but masking their potential for adverse effects as well. Obviously, studies are needed. In addition, certain techniques, such as using a step-down approach to treatment in children with moderate or severe asthma, and dosing in the morning, may ameliorate the growth-suppressive actions of ICS over the long-term.

Nonetheless, alternative asthma therapies may be appropriate in certain children for the treatment of persistent mild-to-moderate asthma, and these agents may be less challenging in terms of achieving a desirable balance between efficacy and safety. The chromones, cromolyn and nedocromil, are safe and well-established therapies that can be used as monotherapy in mild-to-moderate pediatric asthma. The effectiveness of these agents, however, has been questioned in a number of studies. Long-acting β2-agonists such as salmeterol have proven to be effective add-on therapies to ICS, but questions about the development of tolerance and unchecked airway inflammation may influence physicians in selecting these therapies for the pediatric population. Theophylline has proven to be efficacious over many decades, but its safety profile and need for plasma monitoring and dose optimization may burden busy physicians. Several compelling factors support the use of LTRA as primary, controller therapy, and add-on therapy for mild-to-moderate persistent asthma, including established efficacy, good safety profiles, and simple, oral, dosing requirements. These factors should increase adherence and support long-term, well-tolerated efficaciousness in young children with persistent asthma. Direct, long-term comparative studies will be needed in the future to clarify this issue of balancing safety with efficacy.

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