Ann Allergy Asthma Immunol 117 (2016) 595–600

Contents lists available at ScienceDirect

Mini-Symposium - Inhaled Corticosteroids Safety Panel

Inhaled corticosteroids
Effects on growth and bone health

David P. Skoner, MD *,†

* Director, Division of Allergy and Immunology, West Virginia University Children's Hospital, Morgantown, West Virginia
† Professor of Pediatrics, West Virginia University School of Medicine, Morgantown, West Virginia

ARTICLE INFO

Article history:
Received for publication March 18, 2016.
Received in revised form July 19, 2016.
Accepted for publication July 26, 2016.

ABSTRACT

Background: Both slowed growth in children and reduced bone mineral density (BMD) are systemic effects of corticosteroids, and there is concern about the degree to which these systemic effects affect growth and BMD.
Objective: To engage in a data-driven discussion of the effects of inhaled corticosteroids (ICSs) on growth in children and BMD.
Methods: Articles were selected based on their relevance to this review.
Results: Studies of ICSs in children in which growth was a secondary outcome have revealed slowed growth associated with low doses of budesonide, fluticasone propionate, and beclomethasone dipropionate. In the study of budesonide, the effect was permanent, and in the study of fluticasone propionate, the effect was long-lasting, but it is unclear whether the effect was permanent. However, the results of studies in which growth was the primary outcome were mixed. Slowed growth was detected in a study of beclomethasone dipropionate; however, slowed growth was not detected in a study of ciclesonide or flunisolide. A decrease in BMD acquisition in children was associated with high doses but not low to medium doses of ICSs. In adults, there was a dose-related effect of ICSs on BMD. Both higher daily dose and larger cumulative dose were associated with increased bone density loss.
Conclusion: Because of the systemic effects on growth and bone health, children should be monitored for growth using stadiometry every 3 to 6 months and BMD should be monitored yearly in patients being treated with high doses of ICSs.

Introduction

Slowed growth and reduction in bone mineral density (BMD) are known adverse effects of systemic exposure to corticosteroids. Studies have found systemic effects of oral corticosteroids on growth,[1–3] BMD,[4] and risk of fracture.[5] Systemic exposure is reduced when corticosteroids are inhaled instead of taken orally or parenterally. However, although asthma treatment and management guidelines recommend inhaled corticosteroids (ICSs) as the preferred first-line therapy for asthma,[6,7] uncertainty remains among some clinicians about the extent of systemic effects among ICSs. In this article, we discuss the data on ICS systemic effects on growth and bone health.

The effects of ICSs on growth in children and bone health have been extensively reviewed in the past, and several recent reviews[8–11] summarize this area very well. However, some clinicians who do not treat patients with asthma on a regular basis, for example, practitioners in primary care or pediatrics, are uncertain of the balance between ICS efficacy and safety. This article is one in a series of articles in a minisymposium entitled Inhaled Corticosteroids in Asthma: The Balance Between Safety and Efficacy, which was developed to help guide clinicians through identified knowledge and practice gaps concerning the balance of ICS efficacy and safety, the effects of ICS delivery and devices, and the importance of patient education and effective communication. As such, the goal of this article is not to comprehensively review all growth and bone health studies but to highlight key articles for clinicians who might not be familiar with the literature. This article focuses on key, well-designed studies of particular populations of interest. In particular,

Reprints: David P. Skoner, MD, West Virginia University Health Sciences Center, 1 Med Center Dr, Morgantown, WV 26505; E-mail: dskoner@hsc.wvu.edu.
Disclosures: Dr Skoner declares that he has received grant and research support from Genentech, GlaxoSmithKline, Greer, Merck, Novartis, Sunovion, and Teva. Dr Skoner is a consultant for Greer, Meda, Merck, Mylan, Sunovion, and Teva. He also states that he is on a speaker's bureau for Greer, Genentech, Meda, Merck, Novartis, and Sunovion.
Funding Sources: This article was supported by an independent educational grant from Meda Pharmaceuticals Inc.

http://dx.doi.org/10.1016/j.anai.2016.07.043
1081-1206/

this review focuses on well-designed growth studies funded by the National Institutes of Health (NIH) and pharmaceutical industry after issuance of guidance by the US Food and Drug Administration (FDA).

Systemic availability varies among ICSs and depends on an ICS's pharmacokinetics, formulation, and delivery.[11] These effects are discussed in more detail in 2 other articles in this minisymposium (Inhaled Corticosteroids: Ocular Safety and The HPA Axis and Inhalation Devices, Delivery Systems, and Patient Technique). Factors such as receptor-binding affinity, lipid conjugation, protein binding, and clearance from systemic circulation contribute to systemic adverse effects.[11] In addition, drug formulation can affect the proportion of the ICS dose that is delivered to the lungs and systemic availability. In particular, in pressurized metered-dose inhalers (pMDIs), hydrofluoroalkane solution formulations deliver a higher fraction of smaller particles to the distal airways and distribute the drug more evenly throughout the lungs compared with chlorofluorocarbon formulations.[12] The type of device can also affect systemic availability. Evidence suggests that compared with dry powder inhalers (DPIs), pMDIs may enhance lung deposition while reducing systemic bioavailability via the gastrointestinal tract.[13,14] Note that the major source of systemic bioavailability of ICSs is the lung and not the gastrointestinal tract.[15] In addition, ICS bioavailability is affected by the choice of spacers and masks.[16,17] Nebulizers also affect bioavailability, as shown in one of the few growth studies in which an ICS was delivered by nebulizer.[18]

Growth in Children

A frequently expressed concern of ICSs is the systemic effects on growth in children. Growth is considered the most sensitive indicator of systemic corticosteroid activity by the FDA—more sensitive than the hypothalamic-pituitary-adrenal axis.[19] However, detecting effects on growth is confounded by growth rates that vary throughout childhood. Our focus is on high-quality, well-designed studies with treatment durations of approximately 1 year or longer. These include NIH-funded studies that evaluated growth as a secondary outcome and pharmaceutical-funded studies in which growth is the primary outcome to examine the risks of ICSs and compare the relative systemic activities of different ICS.

Studies With Growth as a Secondary Outcome

Three NIH-funded studies with growth as a secondary outcome—Childhood Asthma Management Program (CAMP), Prevention of Early Asthma in Kids (PEAK), and Treating Children to Prevent Exacerbations of Asthma (TREXA)—revealed suppressed growth with low doses of budesonide via DPI, chlorofluorocarbon-propelled fluticasone propionate via pMDI with valved spacer and facemask, and hydrofluoroalkane-propelled extrafine-particle beclomethasone dipropionate via pMDI, respectively.[20–22] In the CAMP trial, the effect on growth was permanent. In the PEAK trial, the growth effect was long-lasting (2 years after discontinuation) in certain subgroups, but children were not followed up to final adult height to determine permanency. All 3 trials were randomized, double-blind, placebo-controlled trials with large sample sizes and used low doses of ICSs. Treatment durations were 4 to 6 years for the CAMP study, 2 years for the PEAK study, and 44 weeks for the TREXA study. Note that the TREXA study, with a study duration of 44 weeks, was an exception to FDA guidance that study durations should be at least 1 year.[19] All 3 studies were designed with efficacy as the primary outcome and growth as a secondary outcome. PEAK enrolled preschool infants and toddlers, whereas the other 2 studies enrolled school-aged children, and certain drivers of growth, such as nutrition, may be more important in the former population.

In the CAMP study, 1,041 children in the United States aged 5 to 12 years with mild to moderate asthma were treated twice daily with 200 μg of budesonide via DPI (Turbuhaler), 8 mg of nedocromil via pMDI, or placebo (via Turbuhaler or pMDI) for 4 to 6 years.[20] The study found a decrease in the change in standing height attributable to long-term ICS treatment, but the effect was transient (Fig 1). Compared with children who received placebo, children who received budesonide grew 1.1 cm less during the study ($P = .005$). Children in the budesonide treatment group had reduced growth velocity in the first year, but in later years growth velocity increased to levels comparable to those of the placebo group. However, this resumed growth velocity could reflect an adherence issue effect in which patients were adherent in the first year but not as adherent in subsequent years, and thus in later years there was less systemic exposure of the ICSs.[23,24] The decrease in growth velocity resulted in a permanent effect on adult height, in which there was a 1.2-cm difference (95% CI, 0.5–1.9 cm) in height 13 years after randomization when the mean age of patients was 25 years.[25]

Comparable results occurred in the PEAK study. In this multicenter study conducted in the United States, 285 children 2 and 3 years old at high risk for asthma were treated twice daily with 88 μg of chlorofluorocarbon-propelled fluticasone propionate or placebo via pMDI with an AeroChamber valved spacer and facemask for 2 years followed by a 1-year observation period without study medication.[21] The AeroChamber with the facemask delivers twice the amount of fluticasone propionate to the lung in young children than with the Babyhaler,[17] which had been used in previous studies and has shown no effects of chlorofluorocarbon-propelled fluticasone propionate pMDI on growth in 1- to 3-year-olds.[26] Treatment with fluticasone propionate was associated with a 1.1-cm reduction in growth at the end of 24 months of treatment compared with treatment with placebo ($P < .001$). However, during the 1-year observation phase, growth velocity was greater in the fluticasone propionate group than in the placebo group, and by the end of the 1-year observation phase the difference in height between groups had decreased to 0.7 cm ($P < .008$). That is, slowed growth was temporary. Two years after the 2-year treatment period ended, there was no significant difference between the fluticasone propionate and placebo groups in change in height from baseline (difference between fluticasone propionate and placebo groups, −0.2 cm; 95% CI, −1.1 to 0.6 cm).[27] However, a post hoc subgroup analysis suggested that the fluticasone propionate effect of slowed growth persisted 2 years after treatment ended in children who were 2 years old and weighed less than 15 kg at baseline (Fig 2). That is, ICSs suppressed growth while being taken, and one subgroup of smaller and younger patients did not catch up after ICS treatment was discontinued like the other subgroups did. However, these results should be interpreted with caution given that this was a post hoc analysis with small sample sizes and observations did not go beyond 2 years after treatment ended. Given these limitations, investigating this result further with a study designed to test the effects of age and weight on ICS use and growth in very young children is warranted.

Similar to the CAMP and PEAK studies, the TREXA study also found slowed growth with ICSs. The TREXA study evaluated the effects of hydrofluoroalkane-propelled, extrafine-particle beclomethasone dipropionate as a daily control, as an intermittent rescue, or as both daily control and intermittent rescue (combined group) vs placebo.[22] In the TREXA study, 843 children aged 5t o 18 years with mild persistent asthma were treated for 44 weeks at 1 of 5 clinical centers in the United States. Growth was 1.1 cm less in both the beclomethasone dipropionate daily control group and the combined group compared with the placebo group ($P < .001$). However, growth in the beclomethasone dipropionate intermittent rescue group was not significantly different from placebo (0.3-cm