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Effects of beclomethasone and factors related to asthma on the growth of prepubertal children

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Summary
Few studies on the concomitant effects of beclomethasone dipropionate and asthma-related factors on the growth of prepubertal asthmatic children have been published to date. In this prospective long-term 'real-life' cohort study we recruited 82 prepubertal steroid-naïve asthmatic patients aged 3 + years, excluding those with birth weight lower than 2500 g, malnutrition, and other concurrent chronic diseases. Height/age and weight/age Z scores were calculated every three months. Random effects multivariate longitudinal data analysis was used to adjust height/age and weight/age Z scores with independent variables. Among the studied patients, 63.4% were male, aged 4.7 ± 1.5 years, 68.3% suffered from severe persistent asthma and had normal values for height/age and weight/age Z scores at enrolment. They were followed for 5.2 years (range 2.3–6.1) and used a mean daily beclomethasone dipropionate dose of 351.8 mcg (range 137.3–1140.0). Height/age and weight/age Z scores were not affected by either duration of treatment or doses of beclomethasone dipropionate up to 500 mcg, 750 mcg and higher than 750 mcg (p-values > 0.17). The multivariate analysis final model showed that severe persistent asthma was associated to lower height for age Z score ($p = 0.04$), whereas hospitalizations because of acute asthma (before and during follow-up) were associated ($p = 0.02$) to lower weight for age Z score. Growth parameters were not affected by the use of beclomethasone dipropionate.

Introduction

An ideal inhaled corticosteroid (ICS) should demonstrate high pulmonary deposition and residence time, in addition to low systemic bioavailability and rapid systemic clearance.[1] Pharmacokinetic characteristics vary for each ICS, and bioavailability of a particular ICS depends on the oral bioavailability and the amount absorbed directly from the pulmonary vasculature. For instance, the oral bioavailability of the most recent generation of ICS

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(budesonide, fluticasone and ciclesonide) is lower than the previous generation (beclomethasone, triamcinolone and flunisolide),[2] which means fewer side effects.

The oral bioavailability of beclomethasone dipropionate (BDP) is twice and four times higher than that of budesonide and fluticasone, respectively.[1] Therefore, it is relevant to assess the long-term repercussions on growth of children under treatment with the different inhaled corticosteroids and in diverse settings.

Medium-term studies have addressed growth between 6 and 24 months of follow-up, while longer term studies have assessed growth for over 24 months and up to adulthood.[3] Given the inherent difficulties in carrying out long-term longitudinal studies with children (including prepubertal ones), the meta-analysis by Allen et al. has reported only 4 studies on the effects of BDP on growth over 3.8 years of follow-up. These 4 studies had a relatively small sample size (from 29 to 52) of subjects older than 7.5 years.[4]

In a review paper, Doull[3] reported only five long-term studies on the effects of ICS on growth. Only one investigated the effects on height of up to 600 mcg/day of BDP in 26 prepubertal children, and reported no detrimental effect.[3,5] However, the study also included younger children aged from 1.1 year, and, it is recommended[2,6] that the assessment of ICS effects on the growth of prepubertal children should include only subjects over 3—4 years, bearing in mind the hormonal and nutritional factors on growth velocity in younger children.[2,6] Moreover, it is worth pointing out that children below this age should, in all cases, be studied separately, and factors such as birth weight and nutrition be taken into account.[6] Likewise, Pedersen suggested that more pediatric safety studies are needed, particularly in young age groups and concerning long-term inhaled corticosteroid therapy.[2]

Prospective long-term (over 24 months) studies assessing simultaneously the effects of BDP on height and weight standard deviation scores as well as asthma features in prepubertal asthmatic children are scarce in the literature. It is well known that because of its relatively lower cost, BDP-CFC is still widely prescribed in developing countries, and that BDP-HFA also has its share in the developed world. Effects of ICS on growth patterns should be studied in diverse settings with different environmental and living conditions, as well as ethnical, genetic, and nutritional aspects. Taking into account these issues, the present study aimed at analyzing the effects of beclomethasone dipropionate (BDP)-CFC and factors related to asthma on the growth of prepubertal children.

Methods

Study setting

The ISAAC Phase Three study has shown that among Brazilian prepubertal children aged 6—7 years, the prevalence of wheezing in the previous 12 months and of severe persistent asthma were 24.3% and 6.1%, respectively.[7]

To face this significant public health issue an asthma management program — the ''Wheezy Child Program'' - was implemented in Belo Horizonte, Brazil, within the municipal health system network and targeted at children and adolescents from underprivileged families. Two of the program's assumptions were that patients with mild persistent asthma should be followed at primary health care facilities and that moderate-persistent severe asthma cases should only be assisted at one out of four outpatient referral clinics (ORCs) by pediatric pulmonologists or allergologists.

Study design, participants, inclusion and exclusion criteria

This ORC-based, prospective 'real-life' observational long-term cohort study, carried out in the Campos Sales ORC from January 2005 to December 2008, included prepubertal steroid-naïve children, with height and weight measurements within the normal range of Z scores, suffering from moderate to severe persistent asthma, aged 3 + years, with a Tanner sexual maturity rating equal to 1,[8] who required regular treatment with inhaled corticosteroids, and who were followed up to the age of 9 (females) or 9.5 (males). For instance, if a boy started BDP at the age of 8, the observation period was interrupted at age 9.5, even if that patient continued on BDP for uncontrolled asthma.

The lower and upper age limits for both sexes were predefined according to recommendations set by Price et al.[6] to avoid influence of sex corticosteroids.[2] Save those who met the exclusion criteria, all the eligible prepubertal patients from the ORC were admitted into the study.

BDP-CFC was (and still is) the ICS standardized by the Belo Horizonte Municipal Health Authority (BHMHA), and was dispensed free of charge to all study participants. It was delivered through a large volume (650 mL) pear-shaped plastic valved spacer (Flumax®, Flumax Medical Equipments, Belo Horizonte, Brazil), also provided free of charge. BDP-CFC and spacers were only dispensed at the pharmacy clinic, and the participants were deemed unable to obtain them elsewhere being from low-income families. Due to budgetary constraints, add-on anti-asthmatic drugs were not provided by the BHMHA. The quality of inhalation technique, checked by trained nurses, was verified at every follow-up visit, and mouth-washing after inhalation was routinely recommended.

Exclusion criteria were pre-defined as follows: prepubertal children with birth weight below 2500 g, current malnutrition (weight less than −2 Z score), chronic diseases and use of systemic glucocorticoids for more than two weeks per year to treat asthma exacerbations.

We recorded growth measurement values (see next topic) at each three month follow-up visit, as well as data on sex, age, monthly family income, mother's schooling level, previous hospitalizations because of acute asthma, emergency room visits, duration of asthma before BDP treatment, BDP dose, and asthma severity.

In a specific form the pharmacist recorded data pertaining to number of canisters dispensed, therapeutic regimen, dates when empty canisters were returned and new ones dispensed, upon which a new inhaler was provided. When the child was not present on the predicted date for canister exchange, he or she was classified as BDP non-user until contacted by the health team and resumed use of ICS. The possibility of a patient acquiring medication