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ORIGINAL ARTICLE

Lack of bone metabolism side effects after 3 years of nasal topical steroids in children with allergic rhinitis

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Abstract This study evaluated the effects on bone mineral status of long-term treatment with intranasal budesonide (INB) spray, using the recommended dose, in pediatric patients with allergic rhinitis (AR). This retrospective, case–control study of 230 prepubertal children with perennial AR, who had used nasal budesonide at a mean daily dose of 100 μg (range, 89–132 μg) for at least 3 years intermittently, was conducted from May 2007 through May 2010. The bone mineral density (BMD) of the lumbar spine was measured by dual-energy X-ray absorptiometry. Levels of serum calcium, phosphorus, alkaline phosphatase (ALP), parathyroid hormone, and osteocalcin were also assessed. The results were compared to sex- and age-matched controls ($n = 140$), who were newly diagnosed children with AR without any corticosteroid treatment. The 230 study patients (145 boys) were aged from 7 to 11 years. The average age (± SEM) was 8.7 ± 0.7 years; the mean (± SEM) steroid dosage used was 73.5 ± 7.0 μg daily, with 65.2 ± 5.2 g total steroid use during treatment. The 140 control patients (90 boys) were aged from 6 to 11 years. No significant differences were observed in BMD ($P > 0.05$) between the study and the control groups. Although mean serum ALP level was higher, and cortisol, phosphorus, and osteocalcin levels were lower, in the treatment group, these differences were not statistically significant. The findings suggest that long-term intermittent treatment for 3 years with INB spray, 50 μg twice daily, for children with perennial rhinitis revealed no negative effect on BMD and associated parameters.

Keywords Intranasal budesonide · Bone mineral density · Allergic rhinitis · Children

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Introduction

Allergic rhinitis (AR) is a chronic inflammatory disease of the upper airways characterized by sneezing, itching, nasal congestion, and rhinorrhea [1, 2] Current guidelines recommend intranasal corticosteroids (INS) as the first-line treatment for moderate to severe persistent AR. INS are effective for nasal symptoms and congestion because of their potent antiinflammatory activity [3, 4]. The efficacy of the currently available INS in AR is well documented, and the low rate of side effects despite extensive use of INS over many years is indicative of the well-established safety of these drugs [5, 6]. Glucocorticoid-induced osteoporosis or reduced bone mineral density (BMD) has been reported with low-dose (5–10 mg/day) or high-dose inhaled corticosteroids [7]; the literature on topical nasal steroids on the mineral status of bone is controversial [8–11]. Although large studies have reported that there was no substantial risk of INS on bone metabolism in patients with AR [12, 13], there are not enough data available for INS

administration and its effects on bone metabolism in the children. This study assessed BMD and the associated parameters in children with perennial allergic rhinitis (PAR) treated for at least 3 years with intermittent nasal corticosteroid budesonide, and compared the findings with those of children with AR who had never received treatment with corticosteroids.

Materials and methods

Study design

In a retrospective case–control study, 230 children with PAR from the authors' pediatric allergy outpatient clinic were enrolled consecutively between May 2007 and May 2010. The diagnosis and the severity of PAR were defined according to the Allergic Rhinitis and Its Impact on Asthma (ARIA) [14] guidelines. Informed consent was given by the family of the patients.

Patients

A total of 270 children who had received intranasal budesonide (INB) intermittently for $\geq$3 years were included in the present study to investigate BMD and associated parameters; 230 patients gave informed consent after the explanation of the study. This group of patients qualified as having PAR if they had at least two rhinitis symptoms requiring treatment for at least 6 months of the year for the previous 2 years and had a positive skin-prick test response to at least one clinically significant perennial allergen (e.g., house dust mites, molds, cockroach, cockroach excreta, animal dander). The children had been seen at the outpatient pediatric allergy clinic at least every 3–4 months for 3–5 years at the time of the present study. Between clinic visits, changes in INB or other AR medications were always made under the supervision of the clinic so that transient changes in treatment during periods of increased AR symptoms were recorded. These recordings made it possible to calculate accurately the average dose of the exogenous corticosteroid during the previous 3 years and the accumulated dose of budesonide. Compliance with nasal steroids was checked at each visit by asking the child and the family about their compliance and by checking medication level in the bottle. These measures allowed an assessment of compliance. The authors identified all prescriptions for INB that had been filled by patients during the past 3 years and studied the risk of current extra exposure to INB. To investigate the exposure to INB according to dose, they calculated the average daily dose of INB by dividing the total quantity (in micrograms) by the days of supply for that prescription. The participants had not received specific immunotherapy, and none of them had asthma requiring the chronic use of inhaled or systemic steroids. None of the children with PAR had nasal structural abnormalities. All the study group patients had been using only one type of nasal steroid, budesonide. The authors have included 140 children who were newly diagnosed with PAR according to the ARIA guidelines [14] in the control group to obtain a sufficient number of patients for comparison. None of these newly diagnosed children had received oral, inhaled, or nasal corticosteroids for >2 weeks. Following the measures obtained for BMD and associated parameters, budesonide 0.05 mg two times daily was initiated in the control group. Age, sex, body height and weight, body mass index (BMI), the presence of bronchial asthma, daily and total budesonide dosage, duration of treatment, history of any incidents (trauma) in the past, time of diagnosis, family history of atopy, and skin test results were recorded for all study group participants. To avoid the confounding influence of some covariates, the following exclusion criteria were used in the present study: >14 days treatment with systemic corticosteroids ever (both groups of children), topical corticosteroids ever applied to 25% of the body surface (both groups), additional nonatopic systemic disease (e.g., disorders of calcium metabolism, spine demineralization, osteoarthritis, metabolic bone disease, anorexia, or obesity), or injuries of the spine with risk of bone density loss (e.g., prior fracture/immobilization), and chronic use of some supplements (e.g., anticonvulsants, nondietary vitamin D, ketoconazole, hormone replacement therapy).

Measures

BMD (g/cm^2) was measured using dual-energy X-ray absorptiometry (DEXA) (GE Lunar DPX Duo Bone Densitometer; Absolute Medical Equipment, Monsey, NY, USA). The densitometer was calibrated daily 30 min after the apparatus was turned on. Quality control was performed using calibration standard and QC phantom. BMD scans of the anteroposterior (AP) lumbar spine/pediatric (L1–L4) vertebrae were analyzed using the World Health Organization criteria for bone mass [15] and the International Society for Clinical Densitometry [16]. *Z* scores were calculated using the reference population provided by the manufacturer. For *Z* score calculation, the patient's BMD is compared with mean BMD of children of the same sex and age and is also expressed as standard deviation (SD).

Morning venous blood samples were taken to assess osteocalcin, alkaline phosphatase (ALP), calcium, phosphorus, and cortisol levels. ALP, calcium, and phosphorus were analyzed spectrophotometrically by a Mega Automatic analyzer (Merck, Tempe, AZ, USA). Osteocalcin,

intact parathyroid hormone (PTH), and cortisol samples were analyzed using an Immulite chemoluminescence immunoassay (Diagnostic Products, Los Angeles, CA, USA).

Ethical approval

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice and was approved by the local Ethics Committee.

Statistical analysis

The SPSS program (v. 11.5; SPSS, Chicago, IL, USA) was used for all statistical analyses. Signal intensities are given in arbitrary units with mean, SD, or standard error of the mean (SEM). General characteristics were analyzed by an independent sample *t* test or a Mann–Whitney test depending on the data and by Pearson chi-square test for category-wise data. To investigate the relative importance of the variables associated with bone metabolism in relation to dependent factors and in cases of any confounding between them, they were fitted together using a multivariate linear regression model to control confounding factors and to determine which characteristics were independent of the total steroid dose of the children with PAR. A P value < 0.05 or odds ratio (OR) with a 95% confidence interval (CI) that did not include 1.00 was considered statistically significant.

Results

A total of 370 children were studied: 230 in the nasal budesonide group and 140 in the control group. Patient characteristics are shown in Table 1. The ages of the 230 study patients (145 boys) were between 7 and 11 years (± SEM, 8.7 ± 0.7) years. The average (± SEM) follow-up time was 42.67 ± 9.86 months (range, 36–56 months). Average (± SEM) height was 138.0 ± 4.9 cm and average weight was 33.4 ± 1.2 kg. The mean total accumulated dose of budesonide for children in the study group was 65.2 mg (range, 56–112 mg), and the mean (± SEM) budesonide dose used was 73.5 ± 7.0 μg daily. The average IgE titer was 347.4 ± 41 kU/l (normal, 0–52 kU/l). All patients had positive skin test results for at least one allergy (see Table 1).

The ages of the 140 control patients (90 boys) were between 6 and 11 years. Average (± SEM) age was 8.4 ± 0.8 years, average height was 136.4 ± 3.7 cm, and average weight was 32.8 ± 1.4 kg; the average IgE concentration was 376.6 ± 31.5 kU/l. All patients had positive skin test results. The two groups were comparable with respect to age, height, and weight. The proportion of males was somewhat higher, and the mean duration of AR at the time of the study was significantly longer, in the budesonide group than in the control group.

BMD parameters and budesonide treatment

Although there was a tendency toward lower levels for mean basal serum cortisol and osteocalcin and higher levels for phosphorus, ALP, and PTH in the study group, there were no statistically significant differences between the two groups ($P > 0.05$). The Z scores and the BMD results of the two groups were also similar ($P > 0.05$) and comparable with the control group ($P > 0.05$; Table 2). Additionally, the authors assessed the body height, weight, and BMI-associated SD scores separately for the two groups. Although a tendency toward lower scores for all parameters was found in budesonide-treated children, none of the comparisons reached statistical significance (see Table 1). Finally, a possible association of the BMD results and the nasal budesonide treatment was analyzed. There was no correlation between the BMD scores and associated parameters and the accumulated or current dose of budesonide (Table 3). The number of times per week that the children participated in sports activities was the same in both groups (budesonide, 1.75; control, 1.60), respectively.

Discussion

The assessment of possible systemic side effects of long-term INS treatment is a central issue in pediatrics, as corticosteroids are prescribed to more patients with PAR and for longer periods of time than ever before [6]. The currently available INS—beclomethasone dipropionate (BDP), budesonide (BUD), flunisolide (FLU), fluticasone propionate (FP), mometasone furoate (MF), and triamcinolone acetonide (TAA)—differ from each other in terms of their systemic absorption, volume of distribution, half-life, and the extent of systemic bioavailability [17, 18]. The systemic bioavailability of the INS is determined by the amount of the drug delivered and subsequently absorbed by the lungs and the amount of drug absorbed from the gastrointestinal tract. For INS, there is a high degree of deposition in the nasal cavity, followed by mucociliary clearance to the throat and, eventually, to the gastrointestinal tract, and absorption from the mucosal surface can contribute up to 50% systemic bioavailability of the INS [4]. Although glucocorticoid-induced osteoporosis is accepted as a major side effect for oral corticosteroid treatment [19], there are not enough data available for long-term treatment with INS and its effects on bone metabolism [20]. Although some publications did not

Table 1 Patient characteristics of the two groups children with allergic rhinitis

	Study group	Control group	*P* value
Number of patients	230	140	
Age, mean (years)	8.7 ± 0.7	8.4 ± 0.6	0.25
Male (%)	145 (63)	90 (64)	0.55
Height, mean (cm)	138.0 ± 4.9	136.4 ± 3.7	0.33
Weight, mean (kg)	33.4 ± 1.2	32.8 ± 1.4	0.16
Skin-prick test positivity to at least one allergen, number of patients	230	140	
IgE (kU/l)	347.4 ± 41	376.6 ± 31.5	0.23
Symptom duration, mean (years)	4.5 ± 0.9	2.2 ± 0.6	
BMI (kg/m^2)	16.52 ± 3.59	17.33 ± 3.10	0.36

Values are given as mean ± standard error of the mean

BMI body mass index

Table 2 Comparision of some bone metabolism-associated parameters between the two groups

Parameters	Budesonide group ($n = 240$)	Control group ($n = 140$)	*P* value
BMD (g/cm^2)	0.46 ± 0.72	0.47 ± 0.50	0.23
Z score (no. patients, %)			
>−1.0	168 (70)	104 (74)	0.61
$-1 > Z > 2.5$	65 (27)	34 (24)	
<2.5	7 (3)	2 (2)	
Calcium (mg/dl)	9.5 ± 1.1	9.9 ± 0.7	0.19
Phosphorus (mg/dl)	5.2 ± 1.5	4.6 ± 0.7	0.24
ALP (IU/l)	490.7 ± 276.5	398.4 ± 260.7	0.42
PTH (pg/ml)	24.9 ± 0.9	22.2 ± 0.6	0.23
Osteocalcin (ng/ml)	63.6 ± 25.9	67.5 ± 32.5	0.45
Cortisol (μg/dl)	8.3 ± 3.64	9.04 ± 4.43	0.36

Values are given as mean ± standard error of the mean

BMD bone mineral density, *ALP* alkaline phosphatase, *PTH* parathyroid hormone

Table 3 Estimates of total steroid dose effect of variables associated with bone metabolism status of the children with perennial allergic rhinitis (PAR) through logistic regression ($n = 230$)

	OR	95% CI
BMD	1.5	0.47–3.68
ALP	0.80	0.48–1.60
PTH	1.3	0.61–2.51
Osteocalcin	1.6	0.55–4.02
Cortisol	1.3	0.90–3.76

OR odds ratio, *CI* confidence interval, *BMD* bone mineral density, *ALP* alkaline phosphatase, *PTH* parathyroid hormone

report proof for significant bone density reduction in children receiving low to medium inhaled corticosteroid doses [21, 22], on the other hand, some publications reported negative effects of ICS on BMD [7, 23].

Although large studies have reported that there was no substantial risk of intranasal steroids on bone metabolism in patients with AR, no new data have been reported in the literature for the past 10 years. The results of the present study corroborate those reported in previously published studies of smaller groups of less well characterized children for shorter periods of time with INS [11, 13]. Schenkel and colleagues [11] examined the effect of intranasal MF on bone metabolism. The treated children had a mean change of 6.95 versus 6.35 cm/year in the placebo. Wilson and colleagues [24] studied 20 patients in a single-blind, randomized, four-way cross-over design and compared the systemic bioactivity of aqueous formulation of BUD, MF, and TAA in terms of bone metabolism and associated markers. The authors found that was no significant difference between the placebo and the active treatments with any of the markers of bone metabolism and associated parameters. Taken together, these studies show a lack of any effect on bone metabolism with INS in pediatric patients.

The effects of the exogenous corticosteroids on bone can be evaluated by biochemical markers of bone metabolism, BMD, or frequency of fractures [25, 26]. The lumbar spine is the ideal site for DEXA scans because of its high content of metabolically active trabecular bone, its propensity for fractures as well as its sensitivity, and changes in the mineral density and bone size in growing children [16, 27, 28]. The results showed no significant differences

compared with control for effects on BMD after 3 years of intermittent treatment with budesonide nasal spray. When designing the present study, the authors tried to avoid some of the problems of interpreting potential findings in the budesonide-treated children. This aim was achieved by restricting the study to well-characterized patients who were known to have not received systemic corticosteroids for >14 days and by including a control group of children with PAR who had never received exogenous corticosteroids. In addition, the technicians who took measurements of BMD were blinded with respect to the treatment given to minimize any possible bias. The BMD results from this study corroborate those of Kemp et al. [29], and they are extended by showing that even the most commonly bioavailable formulation of fluticasone at a relatively high dose does not cause a reduction in BMD at the lumbar spine, the most appropriate and sensitive marker for the skeletal effects of systemic corticosteroid therapy.

Studies of biochemical markers of bone metabolism such as serum osteocalcin may have potential as indicators of the long-term effects of corticosteroids but are less indicative than DEXA regarding the potential for cumulative effects over a 3-year period. In this study, serum osteocalcin values were not statistically different between the two groups. The serum osteocalcin values were highly variable and may not be reliable or predictive of other systemic effects [24]. Another study investigating osteocalcin has reported a significant reduction in children who received ICS [26]. It is unclear whether the individual markers of systemic effects of corticosteroids correlate with each other or which is the most sensitive and predictive of problems in other organ systems. The results of the present study for serum osteocalcin level were not predictive of the changes in the skeletal BMD measurements in children who had used 3-year intermittent nasal budesonide for PAR.

Suppression of the hypothalamic–pituitary–adrenocortical (HPA) axis is one of the methods used to determine if exogenous steroids have potentially negative effects. Reviewing the types of studies and methods used to measure the HPA axis is beyond the scope of this study; however, the authors studied serum cortisol levels in both study and control groups. Serum levels of cortisol in the morning (as in this study) and 24-h urine excretion are methods for the detection of the treatment-induced inhibition of the HPA axis. Single plasma cortisol values in the morning (before dose), as used in this study, provide a momentary value only, and conclusions cannot be drawn regarding the cortisol pattern over 24 h. However, as the values were gathered at the same time in both groups, they are comparable in each individual. It can be concluded that endogen cortisol production is active and that the children treated with budesonide do not show statistically different values from the reference values of the controls. The use of 24-h urinary cortisol provides a more reliable index of the HPA-axis function, as it is not affected by the circadian variations in cortisol secretion [17]. Experience with ICS has shown that changes in the HPA axis function following high doses of budesonide (typically >800 μg in adults and >400 μg in children) are detectable only by means of sensitive biochemical markers and are not usually associated with clinical changes in adrenal function [17]. The authors did not find any significant changes in other biochemical markers of bone metabolism such as serum calcium, phosphorus, ALP, and PTH. Moreover, they did not have a chance to evaluate serum procollagen peptide I levels, another important marker for bone metabolism because of a lack of measurement technique. Dietary calcium intake is another important point to be discussed. Some authors think that decreased BMD may be partly related to calcium intake lower than necessary for the maintenance of an adequate calcium level, while vitamin D intake is thought to be helpful to control the negative side effects of the ICS on bone turnover [30–32].

In conclusion, long-term intermittent usage of nasal budesonide spray at an average daily dose of 100 μg for up 3 years has no statistically significant negative effects on BMD at the lumbar spine and other bone metabolism markers in prepubertal children with PAR. Differences in age- and disease-matched controls were not shown in the markers of bone formation and resorption. The results of this study add to the body of evidence supporting the safety of long-term use INS in children with PAR.

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