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Effect of beclomethasone dipropionate on bone mineral content assessed by X-ray densitometry in asthmatic children: a longitudinal evaluation

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Effect of beclomethasone dipropionate on bone mineral content assessed by X-ray densitometry in asthmatic children: a longitudinal evaluation. ©ERS Journals Ltd 1994.

ABSTRACT: There is little information on bone turnover in asthmatic children taking long-term treatment with inhaled steroids (ICS). The aim of this longitudinal study was to determine the effects of inhaled beclomethasone dipropionate (BDP) on bone mineral density (BMD), in asthmatic children treated over a period of six months.

BMD and growth were studied in two age- and sex-matched groups of asthmatic children. These comprised: 14 asthmatic children (Group 1) who had taken BDP in a dosage of 300–400 μg daily through a 145 ml spacer device for at least 6 months (mean age 9.1 yrs); and a control group of 16 age- and sex-matched asthmatic patients (Group 2) not treated with ICS (mean age 9.5 yrs). Mean duration of asthma was 5.7 yrs in Group 1 and 5.5 yrs in Group 2. Vertebral BMD (L2–L4) was measured by dual energy X-ray absorptiometry (DEXA) at the beginning (baseline) of the study and 6 months later.

There were no significant differences in the baseline bone mass (mean±SEM) between the two groups (0.63±0.03 and 0.64±0.02 $g \cdot cm^{-2}$ in Group 1 and 2, respectively). During the observation period, bone density increased, by 4% (95% confidence interval (95% CI) 2–6) in the control group and by 2.3% (95% CI 0.4–4.2) in the group under BDP treatment, showing no significant influence of the treatment. No difference was found in height velocity evaluated before starting BDP and after 6 months of therapy.

The results of this longitudinal study suggest that the continuous use of inhaled BDP for 6 months (300–400 $\mu g \cdot day^{-1}$) does not cause bone loss, even though, in the treated group, a slightly reduced gain in bone mass was noted. Further studies are indicated to evaluate the effect of higher doses and/or longer treatment with ICS upon bones.

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At present, inhaled corticosteroids (ICS) are by far the most effective anti-asthma drugs available. They have been consistently shown to reduce airway inflammation and bronchial hyperresponsiveness [1]. The currently accepted indications for long-term use of inhaled corticosteroids is the presence of chronic asthma, that is not adequately controlled by nonsteroidal drugs [2]. The use of these drugs is very widespread in Europe, and has recently been supported at an earlier stage in the treatment of asthma [3–5]. Nevertheless, few controlled prospective studies have evaluated whether this form of therapy is associated with long-term side-effects, in particular on bone metabolism of growing children, although research in this direction has been encouraged by many authors [6, 7]. Many studies [6, 8] have looked for changes in the hypothalamic-pituitary-adrenocortical function in children treated with inhaled corticosteroids, yielding contradictory results. A recent study in non-asthmatic subjects showed that low doses (400 $\mu g \cdot day^{-1}$) of beclomethasone dipropionate (BDP) determined a significant reduction in plasma osteocalcin levels, suggesting a possible effect on bone [9]. On the other hand, the results of a recent study in children suggest that asthma itself may cause a reduction in serum osteocalcin [10]. At the moment, it remains largely unknown whether ICS may determine some degree of suppression on bone metabolism, and this issue is particularly important for paediatricians.

The aim of this study is to evaluate the effect of 6 months BDP treatment on bone mineral content of the lumbar spine, evaluated by dual energy X-ray absorptiometry, and the potential risk of impaired bone density in asthmatic children.

Methods

Subjects and protocol

We studied 35 asthmatic children, aged 5–14 yrs, attending our Paediatric Pulmonology out-patient clinic.

All patients had a typical history of episodic breathlessness and wheezing and relief of symptoms with use of bronchodilators. Considering the severity of the children's asthma (number of exacerbations, grade of symptoms, nocturnal awakening, duration of exacerbations) [3, 11], they were divided into two groups: Group 1, suffering from moderate asthma, was continuously treated with inhaled BDP for 6 months; Group 2, suffering from mild asthma served as control. Bone mineral density (BMD) was measured at baseline of the study and 6 months later in all children. After the initial evaluation, subsequent visits and pulmonary function measurements were scheduled at 1–2, 4 and 6 months from the beginning of the study. Of 35 patients enrolled, three were excluded due to aggravation of asthma requiring oral corticosteroids, and two because of poor therapeutic compliance with the study protocol.

Group 1 (BDP group) comprised 14 children suffering from moderate asthma. They were treated with inhaled BDP (Becotide, Glaxo), 300–400 $\mu g \cdot day^{-1}$, divided into two or three doses, for at least 6 months. They had previously been treated with a first line therapy, such as cromolyn, intermittent inhaled BDP and $beta_2$-agonist (salbutamol), but were not sufficiently controlled in terms of clinical symptoms and pulmonary function test. The BDP aerosol was delivered by a metered-dose inhaler, 50 $\mu g \cdot activation^{-1}$. All patients used a 145 ml spacer device (Aerochamber, Trudell Med), with one-way inhalation valve, attached to their inhaler. Parents and children were given precise instructions on the use of the spacer; the technique consisted of a deep inhalation from residual volume to inspiratory capacity, followed by an 8 s breathhold before exhalation. The inhalation technique was checked at each visit and found to be correct in all patients. No patient had been treated with systemic steroids for more than 3 days during the previous 6 months preceding enrolment into the study.

Group 2 (control group) comprised 16 age- and sex-matched asthmatic children, not treated with corticosteroids during the study. The patients of this group suffered from mild asthma, only requiring treatment as needed with inhaled $beta_2$-stimulants. Ten were taking inhaled cromolyn intermittently. None had required oral corticosteroid in the past 6 months.

All subjects regularly attended physical activity at their schools and no one was engaged in competitive sport activities. Regarding habitual diet, none of these children suffered from atopic dermatitis or other conditions requiring particular types of diet. No one was supplemented with calcium or vitamin D.

At each visit, height and weight were measured on the same stadiometer and balance by two trained nurses, and were evaluated by the means of the growth charts of TANNER *et al*. [12]. One girl and two boys from both groups were at stage II according to Tanner's rating of puberty [12]. All other children were preadolescents. None of the patients had any other relevant medical disease, had reported recent bone fractures or suffered from metabolic bone disease. Informed consent was obtained from the parents. The protocol was approved by our Institutional Review Board.

Lumbar spine measurements

Measurements were performed in all patients by a dual energy X-ray absorptiometry densitometer (DEXA) (Sophos-XRA, Sopha Médical, France), which uses as photon source an ultra-stable X-ray tube (operating at 80 kVp±0.05%, 0.4 mA) with K-edge filtration (neodyme oxide). The X-ray beam passes through the filter producing a dual energy spectrum (70 kV-40 kV). The multidetector used 18 natrium lodure scintillators, 18 photomultiplicator tubes and 18 dual channel analysers. The densitometer was calibrated daily using a phantom of known density. Measurements were performed at lumbar spine (L2–L4) in anteroposterior projection. To separate the spinous processes and to prevent the overlaps of bone structures, during the measurement the child was supine, the knees flexed and calves resting on a cushion. The radiation dose to the child was less than 3 mRem (which is about one tenth of the exposure for a standard chest X-ray) [13]. The scanning time for the region of interest (L2–L4) was 2–4 min. The reported coefficient of variation on repeated measurements is about 0.5% *in vitro* and less than 1% *in vivo* [14], and in our laboratory (preliminary results) it is 0.9% in healthy children.

All images were processed blind by the same investigator (MCB). The system scans the lumbar spine in a rectilinear way and the results are expressed as bone mineral density (BMD) in $g \cdot cm^{-2}$. To compare the results to those found in a reference population, values of BMD were expressed as percentage predicted for age (x) using a regression equation ($BMD=3.86\times10^{-4}x^3-8.18\times10^{-3}x^2+7.46\times10^{-2}x+0.336$) obtained from GLASTRE *et al*. [13] using the same DEXA technique in healthy children.

Lung function tests

Lung function tests were performed using a dry bell spirometer (Pulmograph, Sensor Medics, CA, USA). Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and forced expiratory flow between 25–75% of vital capacity ($FEF_{25-75\%}$) were measured at each visit. Each child performed at least three forced expirations from full inspiration in the standing position and the best was accepted [15].

Statistical analysis

Student's paired t-test was used for the evaluation and comparison of the results obtained in each group at the beginning of the study and 6 months later. Comparisons between groups were obtained using unpaired Student's t-test. BMD inter- and intragroup correlations were evaluated by analysis of variance. Regression analysis was used to evaluate the correlation between BMD and age. Results are expressed as mean±SEM. A probability of $p<0.05$ was considered significant.

Results

All 14 children from Group 1 completed the 6 months BDP therapy. Demographic data of the two groups are presented in table 1. There were no significant differences between the two groups in age, height, weight and body mass index. Duration of the disease was not different in the two groups.

Table 1. – Physical and clinical characteristics of the study population

	Group 1 (n=14)	Group 2 (n=16)	p
Age yrs	9.1±0.6	9.5±0.7	NS
Sex M/F	11/3	11/5	
Height cm	135±4	137±3.9	NS
Weight kg	33.6±3	35±2.9	NS
BMI kg·m^{-2}	18.4±0.74	18.2±0.68	NS
Duration of asthma yrs	5.7±0.3	5.5±0.6	NS
FEV_1 % pred	78±4	96±3	<0.01

Values are expressed as mean±SEM. Group 1: inhaled BDP. Group 2: controls. BMI: body mass index; FEV_1: forced expiratory volume in one second; BDP: beclomethasone dipropionate; NS: nonsignificant; % pred: percentage of predicted.

There were no significant differences (p=NS) in the baseline bone mineral density between the two groups (0.63±0.03 and 0.64±0.02 g·cm^{-2} in Group 1 and 2, respectively). With respect to reference values [13] initial mean BMD was 98±3.9% in Group 1 and 97±1.9% in Group 2. The relationship between the BMD and the age of children was r=0.69, p<0.001. During the observation period, bone density increased by 4% (95% confidence interval (95% CI) 2–6) (p<0.01) in the control group and by 2.3% (95% CI 0.4–4.2) (p<0.05) in the group under BDP treatment (fig. 1). After 6 months of therapy, mean values of BMD were 0.65±0.02 and 0.67±0.02 g·cm^{-2} in Group 1 and 2, respectively. Analysis of variance did not show any significant influence of the treatment on BMD values between the two groups (p=0.43, F=0.6).

Mean FEV_1 was significantly lower (p<0.01) in group 1 than in group 2 at entry to the study (table 1). Expressed as percentage of predicted value [16], FEV_1 increased significantly from a mean of 78±4% before BDP therapy to 94±4% and 88±3% after 1 and 6 months of therapy, respectively, (p<0.001) in Group 1. After 6 months mean % FEV_1 of Group 2 was 92±3% (p=NS).

The height percentile ranged from 10–97 and weight percentile from 10–97 in both group. The mean height velocity evaluated at the entry of the study was similar in both groups (6.5 cm·yr^{-1} in Group 1 and 7 cm·yr^{-1} in Group 2 p=NS). In the treated group, no difference (p=NS) was found in height velocity evaluated before starting BDP (6.5 cm·yr^{-1}) and after 6 months of therapy (6.6 cm·yr^{-1}).

Discussion

The results of this study suggest that therapy with inhaled BDP (300–400 µg·day^{-1}) does not cause bone density loss in asthmatic children treated over a period of six months.

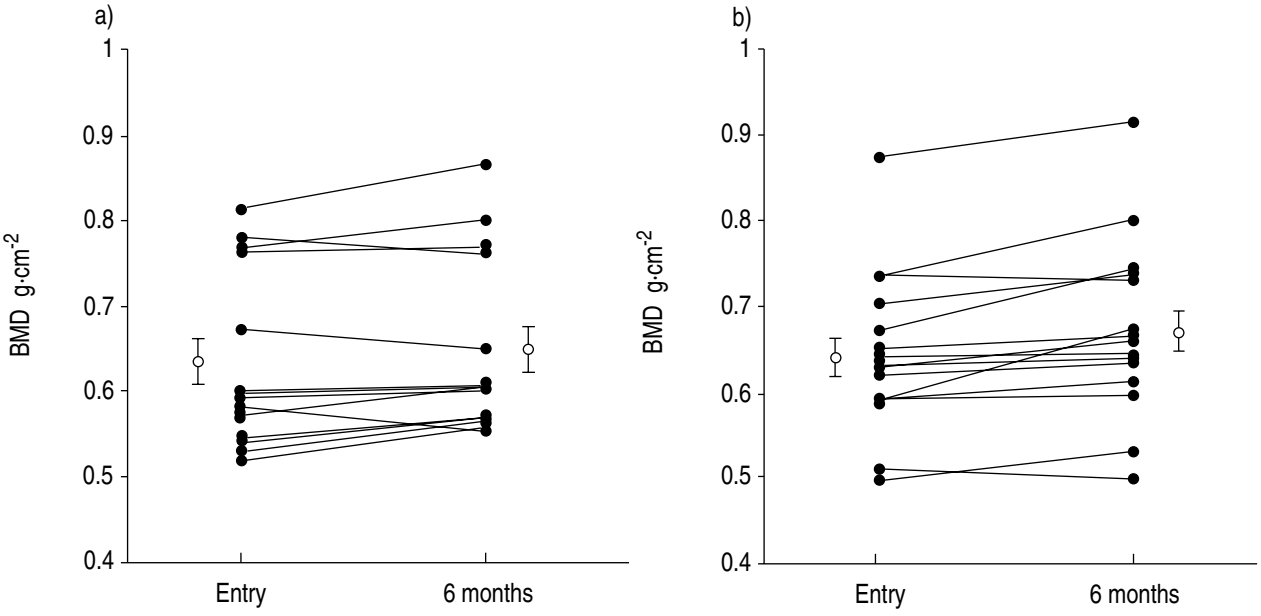

Fig. 1. – Individual results of BMD: a) in children treated with BDP (Group 1); and b) in controls (Group 2) at the start and at termination of the study. During the observation period, mean BMD increased significantly both in BDP group (p<0.05) and in control group (p<0.01). Open circles indicate mean values and vertical bars represent ±SEM. BMD: bone mineral density; BDP: beclomethasone dipropionate.

Long-term systemic steroid therapy in asthmatic patients is associated with decreased trabecular bone density, and osteoporosis has been found to occur in 10–40% of patients [17, 18]. Some authors [6] report evidence indicating that the use of inhaled steroids in adult patients may also play a part in the development of osteoporosis, although recent preliminary data do not confirm this possibility [19]. It is, however, known that the magnitude of the effect of ICS on mineral metabolism is significantly less than that of therapeutically equivalent doses of oral steroids [20].

ICS are clearly effective in improving the control of asthma and lung function, and they are considered an established and safe mode of therapy [21]. They are often prescribed for months in asthmatic children. Nevertheless, to our knowledge, no longitudinal study has focused on the possible long-term effect of ICS therapy on bone density in asthmatic children, and no clear "dose and time threshold" have been established to safely exclude this occurrence.

The baseline results of our study show that both groups presented comparable values of bone density that were within the range of a paediatric reference population [13]. The severity of the disease was not the same in the two groups but, for ethical reasons, it was not possible to inadequately treat patients with moderate asthma. The finding of normal values of BMD is consistent with an earlier study of HOPP *et al.* [22], who showed normal BMD in 15 asthmatic children when compared with healthy controls. This disagrees with the observations of RUEGSEGGER *et al.* [23], who found that the BMD of asthmatic patients never having received inhaled or oral corticosteroid tended to be lower than the values of healthy controls.

We found no significant differences in the baseline mineral content between the treated and untreated group. These data and the successive longitudinal evaluation should eliminate the confounding effect of past booster courses of systemic corticosteroid, which is the most important criticism directed to cross-sectional studies [6]. The longitudinal results of our study suggest that continuous treatment with inhaled BDP (300–400 $\mu g \cdot day^{-1}$) over a period of 6 months did not determine bone loss. The treated group, in fact, presented a slight but significant improvement in bone density after the period of treatment, as did the control group (fig. 1). Nevertheless, we think that this is not sufficient to exclude effects of ICS treatment upon bones; since, bone density is known to increase during normal growth, and as we are dealing with growing children, we have to consider the possibility that treatment could determine a slowing in skeletal maturation. This effect may be speculated by evaluating the lower average percentual gain in bone density noted after 6 months in the treated group (2.3%) with respect to control group not inhaling steroids (4%). We do not know the clinical relevance of these data in the long-term, and, because of the low number of subjects studied, we are aware that the statistical power of our analysis does not allow definitive conclusions, and that further research is needed.

It is very important to achieve an optimal bone mass during childhood [24]. Peak bone mass of the adult, usually achieved in the third decade of life, is in fact a function of bone mass attainment during adolescence, and all of the factors affecting bone density in children are important determinants of the subsequent risk of osteoporosis [13]. Once the peak bone mass has been reached, the normal loss in bone density is about 1% per year.

Recent evidence suggests that even if small doses of inhaled budesonide do not affect adrenal function [25], they are able to decrease markers of bone formation [26]. Similar results are described by TEELUCKSINGH *et al.* [9], demonstrating that doses of 400 μg of BDP daily in healthy adults were associated with reduced serum osteocalcin values (a marker of osteoblastic activity). PACKE *et al.* [27], evaluating vertebral bone density in asthmatic adults receiving high dose inhaled BDP and intermittent courses of systemic steroids, demonstrated a significantly increased bone loss in comparison to patients not inhaling steroids. In contrast, WOLFF *et al.* [28], in a pilot study, failed to find a bone mass reduction in five adult patients treated with BDP for more than 3 yrs. KONIG *et al.* [10], in a cross-sectional study, reported that doses of up to 800 μg BDP do not affect bone density in asthmatic children, but they did not perform a longitudinal evaluation with each patient serving as his/her own control.

Glucocorticoids exert multiple effects on calcium metabolism, but the exact measure and time course of these effects are still to be clarified. It is known that during steroid therapy bone loss occurs mainly at sites in the skeleton where there is a high concentration of trabecular bone, such as the spine and ribs [29]. Trabecular compartment is in fact far more metabolically active than cortical bone. The mid-lumbar spine, therefore, is an ideal site for monitoring metabolic bone disease, such as osteoporosis due to glucocorticoid administration, renal disease *etc.* [30, 31]. For this reason, we decided to use DEXA. This method offers the advantage of being the newest method currently available for the *in vivo* quantitation of BMD [10], and it has been shown to be a precise and accurate technique from the newborn to the adult [24, 32]. Because of low irradiation exposure and high precision, DEXA is to be considered a noninvasive method which is well-adapted to the child [13], and would be useful to define those patients at higher risk [30], such as growing children [24], and to monitor those patients in whom a long-term steroid treatment is expected [28]. In a longitudinal study, JOHNSTON *et al.* [33] demonstrated that calcium supplementation had a positive effect on the rate of increase in bone mineral density in healthy growing children. It will be important to determine whether calcium supplementation could also be a useful preventive strategy in asthmatic children under long-term treatment with ICS.

In conclusion, our findings indicate that the use of 6 months inhaled BDP (300–400 $\mu g \cdot day^{-1}$) does not determine bone loss; even though a slightly reduced gain in bone mass, with respect to the control group, was noted. We think that further research is needed to evaluate the long-term (in years) safety of ICS therapy

on bone. Following BMD measurements in asthmatic children in whom a long-term treatment is expected might be useful to guarantee the safety of this treatment.

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