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Letters to Editor

To the Editor: Effect of Short-Course Budesonide on the Bone Turnover of Asthmatic Children

Inhaled corticosteroids are the most effective therapy for all types of asthma and for patients at all ages; few serious side effects have been reported.[1] With increased use of these drugs for prophylaxis, renewed attention has focused on the risk of adverse effects on growth and bone calcium turnover. This is of particular concern in growing children.[2–5] The osteocalcin (OC) level has been established as a sensitive marker for monitoring bone formation and might serve as a serum marker of actual growth velocity.[6] Previous studies in adults have shown a dose-related decrease in OC levels during short-course treatment with inhaled corticosteroids.[7–8] Beclomethasone dipropionate (BDP), even at a dosage of 400 μg/day, has been associated with reduced OC values.[7] Little is known, however, about the influence of inhaled corticosteroids on bone turnover in children. Studies on this issue have been associated with methodological problems, and conflicting results have been reported.[2–4] The principal aims of our study were: (1) to measure variations of OC levels in asthmatic children and a normal control group, and (2) to investigate the effects of two-weeks treatment with inhaled BUD at low doses (400 μg/day) and high doses (≧800 μg/day), and of prednisone (PRED) at bioequivalent doses on serum OC concentrations.

Forty children were enrolled who were diagnosed with moderate to severe asthma. Their age ranged from 6 to 8 years and there was a male-to-female ratio of 1:1. All subjects received continuous nonsteroidal prophylactic agents and used β_2-agonists both regularly and intermittently. None received treatment with inhaled or oral corticosteroids for 2 months prior to the study. Twenty healthy children, ten boys and ten girls, age 6 to 8 years, served as a control group. In the first part of this study, OC values were assessed in both groups. Blood samples were taken at approximately 2 PM on the first day. In the second part of this study, the 40 asthmatic children were randomly divided into four groups (five boys and five girls in each group): Group I: placebo; Group II: PRED 2.5 mg/day; Group III: BUD 400 μg/day (low BUD); and Group IV: BUD ≧800 μg/day (high BUD). Medications were administered for two weeks and OC levels were rechecked at 2 PM on the fifteenth day. All serum samples were immediately frozen at −70°C until they could be tested. OC was determined by fluoroscent enzyme immunoassay (Pharmacia CAP System Osteocalcin FEIA). The assay measured only intact OC. All samples were tested in duplicate on two separate occasions. The sensitivity of the assay was 0.5 μg/L and the intra and interassay coefficients of variation were 6.6% and 4.1%, respectively.

Statistical analysis was performed by SAS (Statistical Analysis System.) Changes within each treatment group were evaluated by Student's paired *t*-test. Differences between groups were assessed by analyses of variance (ANOVA). Results are shown in Table 1 and Figure 1.

In normal children, levels of OC vary with gender, age, and pubertal stage and they show variations with diurnal and circadian rhythms, with the lowest values in the morning and the highest late at night.[9] There were no significant gender differences in our age group of 6 to 8 years, and their OC levels remained steady until they started to surge in early puberty.[6] In the present study, blood was sampled at approximately 2 PM to minimize the influence of the circadian rhythm on the variability of OC levels.[2]

The OC levels of asthmatic children were much lower than normal subjects (Table 1; $P = 0.0002$). Similar results have been shown in a previous study.[3] It is known that children with severe asthma may suffer from stunted growth even if no corticosteroids are given. The reason for this is unclear, but may be attributed to inadequate nutrition, decreased activity, frequent infections, psychological distress, etc.[6]

Assessing the relative potency of inhaled BUD and oral PRED is difficult. Toogood et al.[10] observed that BUD 26 μg/kg/day (about 2 mg/day) in adults had a level of systemic activity, when assessed by its inhibition of OC production equivalent to about 15 mg of oral PRED per day administered as a single morning dose in adults.

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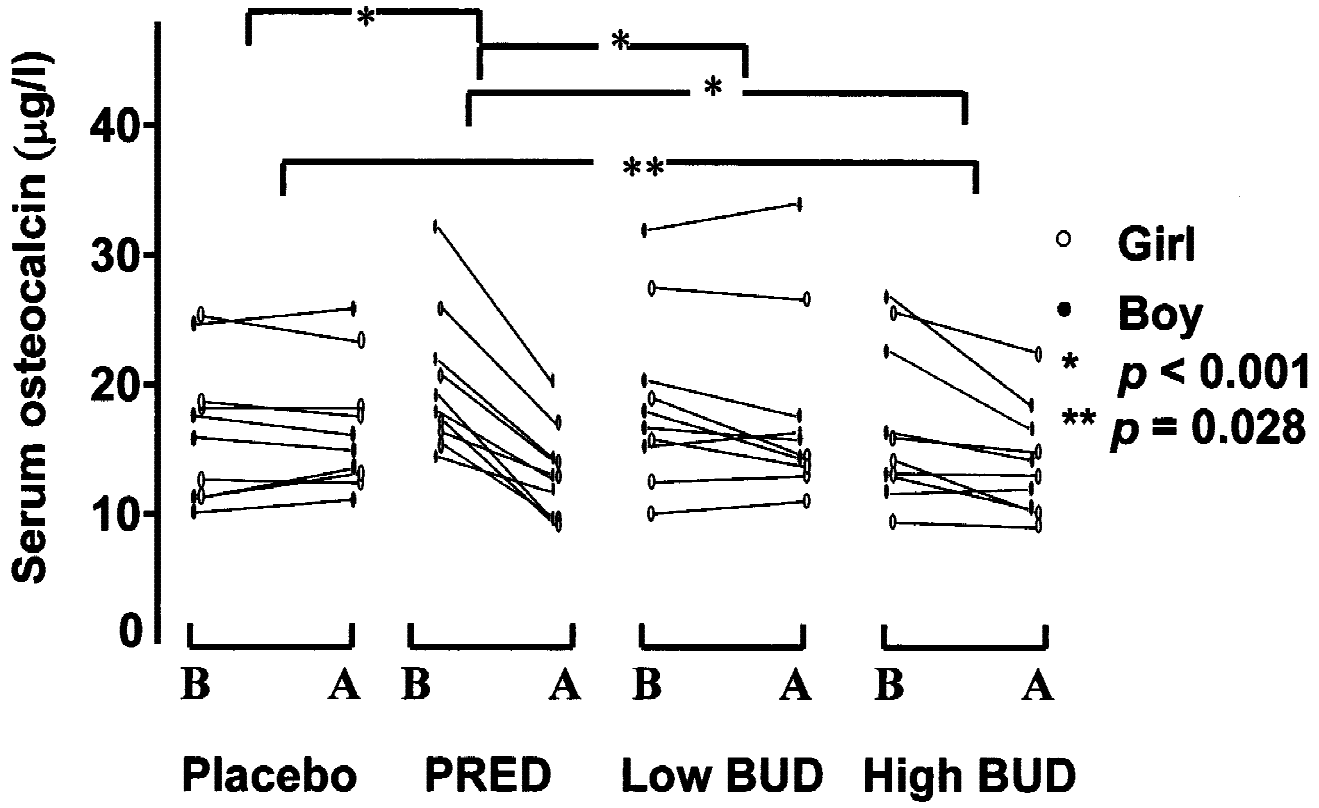

Fig. 1. Changes of osteocalcin levels in each treatment group and treatment difference between groups.

TABLE 1—Mean (±SD) Serum Osteocalcin of Normal and Asthmatic Group Before (Part I) and After Treatment in Each Group (Part 2)

Group	Osteocalcin (μg/L)		*P*
Part I			
Asthmatics	19.22 ± 6.57		
Control	24.91 ± 8.17		0.0002 (Asthmatics vs. control)
Part II	Before	After	
Group I: Placebo	16.46 ± 4.98	16.47 ± 4.34	NS
Group II: PRED	18.65 ± 5.78	11.74 ± 3.32	0.0001
Group III: Low BUD	19.22 ± 6.57	18.53 ± 7.10	NS
Group IV: High BUD	16.80 ± 6.03	14.38 ± 4.20	0.0027

Values are given as mean ± SD.
NS = not significant.

Abbreviations

ANOVA	Analysis of variance
BDP	Beclomethasone dipropionate
BUD	Budesonide
OC	Osteocalcin
PICP	Carboxypropetide typ I procollagen
PRED	Prednisone
SAS	Statistical analysis system

There are no comparable data currently available for children. We estimated that the bioequivalent potency of oral PRED 2.5 mg is between BUD 400 μg and BUD 800 μg in this study.

The main finding of our study was that in a 2-week period low inhaled BUG (400 μg/day) was not associated with a significant reduction in OC levels. High BUD doses (≧800 μg/day) affected OC levels slightly, but less than a dose of 2.5 mg/day of oral PRED. The reason why low inhaled doses of BUD affected OC levels in adults but not in children is not clear. The fact that hepatic clearance of inhaled corticosteroids is significantly faster in children than in adults suggests that children may tolerate relatively higher doses.[2–3] This also explains why high BUD doses affected OC levels in adults, but not in children.[2–3,7–8] Other possible reasons are related to different patterns of bone metabolism in adults and children. Remodeling of bone in adults represents about 98% of the total bone turnover, and modeling only 2%. In contrast, modeling is the major activity of the skeleton in children, who increase their bone mass throughout childhood. OC levels may be a poor marker for inhaled glucocorticoid effects on osteoblasts, which are mainly engaged in bone modeling in children.[2–3] In our study, oral PRED 2.5 mg/day had a greater effect on OC levels than 800 μg inhaled BUD; it was anticipated that 800 μg/day BUD would have a greater effect than 2.5 mg of oral

PRED. In other words, the effect of inhaled BUD on skeletal metabolism was significantly less than that of therapeutically equivalent doses of oral PRED, as has been suggested in previous reports on adults.[8,10] It is possible that the bioequivalent potency ratio of PRED:BUD, measured by its inhibition on OC production, might be higher in children than in adults. It appears that children can tolerate much higher doses of BUD than adults, with a sparing of systemic activity.

Previous reports have shown that inhaled BUD at 800 μg/day for 2 weeks was not associated with a reduction of OC levels,[2] while the same dose for 1 month showed a reduction.[4] Our study noted that inhaled BUD ≧800 μg/day for 2 weeks did affect OC levels to some extent. Based on our findings we speculate that a dose of 800 μg/day of inhaled BUD for 2 weeks might be the maximum dose for children with asthma.

We conclude that inhaled BUD in doses up to 400 μg/day does not seem to affect bone metabolism in children with asthma. Considering the risk of adverse effects on bone turnover, we suggest that children with asthma can take an inhaled dose of BUD of up to 800 μg/day, and such a dose is preferable to oral PRED 2.5 mg/day during short-term treatment. Further studies are needed to determine whether and to what extent the changes in biochemical markers of bone turnover actually signify a clinically important risk for osteoporosis or bone growth after long-term use of inhaled corticosteroids. More sensitive markers, such as carboxypropeptide type I procollagen (PICP), together with other markers of bone resorption,[1] might provide additional information about net bone turnover in asthmatic children treated with inhaled corticosteroids.

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To the Editor: Clinical Observations on Catch-up Growth in Asthmatic Children Following Withdrawal of Inhaled Glucocorticosteroids

Bronchial asthma has been associated with growth retardation in children. Both the disease per se[1] and the medications used to control the inflammatory process[2,3] have been considered responsible for impaired growth.

We have recently shown growth retardation in prepubertal children receiving inhaled glucocorticosteroids for asthma.[4] To evaluate whether catch-up growth occurs when glucocorticosteroids are withdrawn, we analyzed the growth of 30 prepubertal children (24 boys and 6 girls) who were treated and followed because of bronchial asthma in the Department of Pediatrics, Tampere University Hospital. The children had received treatment either with inhaled beclomethasone dipropionate or budesonide as dry powder or spray. The average dose of inhaled glucocorticosteroids was 500 micrograms (range 150−2,000) per square meter of body surface area per day. Due to deceleration of growth velocity over a period of at least 2 years while on treatment, inhaled steroids were changed to a nonsteroidal alternative–inhaled cromolyn sodium. The heights of these children were measured 1 year before, at the time of change of the medication, and after 1 year of nonsteroidal anti-inflammatory therapy. The height measurements were performed at visits to the outpatient clinic by the same nurse, using the same anthropometer. The height standard deviation scores (HSDS) were calculated as: HSDS = X-X'/sd, where X is the patient's measured height and X' and sd are the age-matched Finnish population mean height and