Bone density in asthmatic patients taking inhaled corticosteroids: comparison of budesonide and beclomethasone dipropionate

ABSTRACT—We assessed bone mineral density (BMD) in 20 asthmatics who had been taking inhaled budesonide (BUD) (median daily dose 800 μg) for over a year, 13 of whom had taken previous courses of systemic steroids. Their results were compared with those of 20 patients receiving inhaled high-dose beclomethasone dipropionate (BDP) (median daily dose 1,000 μg), all of whom had received previous courses of systemic corticosteroids, and with those of 17 mild asthmatics who had never taken either inhaled or systemic steroids. Mean (standard deviation) (SD) BMD in the patients taking BUD was 139.5 (28.6) mg/ml. This was significantly lower (p < 0.05) than in the control patients who had never taken inhaled or systemic steroids (160.4 (27.4) mg/ml). Mean BMD in the patients taking BUD did not differ significantly from that observed in patients taking BDP (127.5 (22.6) mg/ml). Although the reduction in BMD in the asthma patients taking regular high-dose BUD could have been due to previous courses of corticosteroid, the magnitude of bone loss is similar to that seen in patients taking high-dose inhaled BDP and intermittent corticosteroids.

The recognition that asthma is principally an inflammatory disease of the airways has laid increasing emphasis on the use of inhaled corticosteroids in preventive measures, and higher doses of inhaled steroids have been recommended in patients unresponsive to lower doses [1]. However, concern has been expressed about the possible side effects of high-dose inhaled corticosteroids [2,3].

We have previously demonstrated reduced bone mineral density (BMD) in asthmatic patients taking high-dose inhaled beclomethasone dipropionate (BDP) in a daily dose of 1,000 μg or more together with intermittent courses of systemic steroids [4]. The degree of bone loss was similar to that in patients taking a combination of high-dose inhaled steroids and continuous low-dose systemic corticosteroids. These findings support those of an earlier study demonstrating a minor increase in bone loss in patients receiving inhaled BDP in a mean daily dose of 400 μg [5].

Budesonide is another inhaled topical steroid commonly used in the treatment of asthma. However, few studies have compared the effect of inhaled BDP and BUD on BMD and metabolism in patients with asthma. We therefore assessed BMD in a group of asthmatic patients taking regular high-dose inhaled BUD and compared it with that of patients taking high-dose inhaled BDP and a group who had never taken corticosteroids by inhalation or systemically.

Methods

We investigated 20 asthmatic patients who had regularly taken inhaled BUD in a median (range) dose of 800 μg (800–1,600 μg) for at least a year. Eighteen patients were taking BUD via a pressurised aerosol, seven of whom were also using a large volume spacer device (Nebuhaler); two patients were taking BUD via a dry powder inhaler. All the female patients were premenopausal. No patient had previously taken BDP, either in the form of a lung or nasal inhaler, or regular systemic corticosteroids.

The results obtained from the patients taking BUD were compared with those from two groups of patients [4]:

- 17 mild asthmatics who had never taken either inhaled or systemic steroids,
- 20 patients taking high-dose inhaled BDP, all of whom had previously taken intermittent courses of systemic steroids for exacerbations of their asthma.

Demographic data and details of treatment in the three groups of asthmatics are shown in Table 1.

In Grampian, data of patients referred for outpatient diagnosis or management of asthma are entered on a computer database (Patient Record System) which is updated at each subsequent clinic review. The 20 patients taking regular inhaled BUD were selected from this database which contains...
details of duration and dosage of inhaled steroid and the number of oral steroid courses taken. The duration of inhaled steroid therapy was similar in the two groups but the median dose of inhaled steroid was significantly greater in the BUD group than in the BDP group.

BMD was measured by quantitative single-energy computer tomography of the lumbar spine which measures only the trabecular component of the vertebrae [6]. The average value for lumbar vertebrae L1 - 3 was calculated and expressed in mg/ml. The precision of the technique was assessed by performing duplicate measurements every four weeks on 10 normal subjects, which gave a coefficient of variation of 0.98%. BMD evaluation was carried out without knowledge of the group to which the patient belonged. Values were expressed as absolute bone density, and as a Z-score (the number of standard deviations from the mean of a reference population, taking into account age and sex [7]). Spirometry was carried out with a dry bellows spirometer, and the patients' level of weekly activity was graded using a validated scale of 1–4 [8].

Bone formation was assessed by measuring serum osteocalcin using an ‘in-house’ enzyme-linked immunooassay described previously [4,9]. The intra-and inter-assay coefficients of variation were less than 6% and less than 10%, respectively. Urine was analysed for the pyridinium cross-links, pyridinoline and deoxypyridinoline, as an index of bone breakdown [10,11].

Student’s unpaired t-test was used to compare means for normally distributed data, otherwise the Mann-Whitney U-test was used to make comparisons between groups.

All patients gave informed written consent to participate in the study which was approved by the Grampian Joint Ethical Committee.

Results

The two groups of patients taking BUD or BDP were matched in terms of age, level of activity and severity of asthma as judged by FEV1. Examination of baseline characteristics among the three groups of patients showed that mean FEV1 was lower in the two groups of patients taking inhaled steroids than in the asthmatics taking no steroids (Table 2).

Mean BMD was lower in the 20 patients on high-
dose BUD than in the patients taking no steroids (Table 2). This difference was more obvious when the values were corrected for age and sex (Fig 1). Similarly, the mean BMD in 20 patients taking high-dose BDP was less than in the control group.

Although the dosage of inhaled steroid in the BUD group was significantly lower than in the BDP group, the mean BMD values did not differ significantly. Correcting BMD values for budesonide dosage (Fig 1) by covariate analysis did not change this relationship ($p = 0.61$).

Seven patients taking BUD had never taken systemic or other inhaled corticosteroids. Their BMD was 147.8 mg/ml, which was lower than but not significantly different from the value of 160.4 mg/ml observed in the patients who had never taken systemic corticosteroids. There was no significant difference in BMD in the 13 patients taking BUD who had previously taken systemic corticosteroids and the seven patients on BUD who had never taken systemic corticosteroids (155.0 mg/ml, Z-score 0.46, and 147.8 mg/ml, Z-score 0.93, respectively). All the patients taking high-dose inhaled BDP had taken systemic corticosteroids at some stage.

There were no significant differences between the three groups in measurements of bone turnover, as judged by serum alkaline phosphatase, serum osteocalcin and urinary pyridinium cross-links (Table 2).

**Discussion**

The effects of systemic absorption of high-dose inhaled BUD and BDP have been the subject of several comparative studies. Significant absorption of exogenous steroids results in suppression of adrenal function; since the latter is relatively easy to measure, most studies have used tests of adrenal function as a surrogate measure of the systemic absorption of inhaled corticosteroids. Several studies have shown that high-dose inhaled BDP causes greater suppression of adrenocortical function than BUD in equivalent dosage [12-14]. The observed differences have, however, been small and of doubtful clinical significance. Other studies have not demonstrated such a difference [15-17].

Caution should be exercised in extrapolating these results to the effect of inhaled corticosteroids on other tissues [3]. Similar results have been observed in the few studies that have compared the effect of BUD and BDP on bone metabolism, with BUD apparently having less effect than BDP. Ali et al [18] showed an increase in the urinary hydroxyproline/creatinine ratio, and a fall in serum alkaline phosphatase in eight healthy volunteers receiving BDP 2,000 mg daily for one month. These results imply an increase in bone resorption and a decrease in bone formation. However, similar changes in biochemical markers were not seen in eight healthy subjects, taking BUD 1,800 mg daily for an equivalent period. The indices of bone metabolism used are relatively insensitive markers of bone turnover [19] and small changes induced by BUD may not have been detected. A similar study was carried out by Jennings et al [20] in 39 normal subjects. This was a cross-over study comparing the effects of inhaled BDP and inhaled BUD, both given for one month in a daily dose of 2,500 mg. Serum osteocalcin and alkaline phosphatase levels fell while patients were taking both steroids but these reductions were greater in patients on BDP. The urinary hydroxyproline/creatinine ratio was also significantly greater on BDP. There was an increase in serum phosphate levels on both drugs, while serum calcium and urinary calcium levels were unchanged. A further dose-response study by the same authors showed that the fall in serum osteocalcin caused by BUD was dose-dependent [21]. Two other studies in which inhaled BUD alone was investigated have also demonstrated falls in osteocalcin levels [22,23].

Systemic absorption of inhaled corticosteroid taken via a metered dose inhaler is minimised if a large volume spacer is attached to the inhaler. Brown et al [24] showed that inhaled BDP taken in a dose of 2,000 mg daily over two days by healthy adults, however, resulted in a fall in osteocalcin levels, suggesting that systemic absorption of BDP inhibits bone formation. This effect was abolished when the BDP was taken
through a large volume spacer. BUD had no effect on osteocalcin levels, irrespective of whether or not the inhaler was attached to a spacer device.

The results of the present study indicate that inhaled BUD is associated with lower BMD than is found in patients not taking regular inhaled steroids, and also suggest that inhaled BUD and BDP have similar long-term effects on BMD, but this study does not have the power to detect differences in BMD smaller than 0.8 SD above or below the predicted mean value for age and sex. These results diverge from previous studies which suggest that BUD has less effect on bone turnover. However, the present study differs in two important respects.

First, asthmatic patients were studied rather than non-asthmatic subjects. Our aim was to investigate BMD in asthmatics receiving treatment given according to current conventional practice. The patients taking BUD and BDP were well matched in terms of age, activity and severity of asthma. However, because of the cross-sectional design of the study, the effect of confounding variables such as previous courses of oral high-dose prednisolone could not be fully taken into account. Our patients had taken regular inhaled steroids for between one and 10 years and their total cumulative dose of oral steroid over this period is not known. However, for those on daily steroid therapy, it is likely that the initial daily dose is a greater determinant of risk of osteoporosis than is the cumulative dose [25]. Mean BMD in the seven patients taking high-dose BUD who had never taken systemic corticosteroids was approximately mid-way between that in the asthmatics who had never taken inhaled or systemic steroids and in the patients taking BUD who had taken systemic corticosteroids. This suggests that the fall in BMD in the BUD group as a whole could be due to the combined effect of inhaled high-dose BUD and previous systemic corticosteroids.

Secondly, if changes in BMD observed in the present study are due to inhaled corticosteroids, they will represent the changes induced by this treatment over several years. Most previous studies on the effect of inhaled corticosteroids on bone metabolism have been short-term studies in non-asthmatic subjects.

Might the bone loss caused by corticosteroids be a short-term effect [25]? Later, compensatory mechanisms might ensure that bone formation and resorption return to equilibrium after bone loss has reached a certain level, but fail to restore the bone mass lost earlier. This could explain why, in the present study, bone density was reduced in both groups of patients taking inhaled corticosteroids but their indices of bone turnover were normal. These results suggest that both high-dose BUD and BDP are associated with reduction in BMD. Longitudinal studies of bone metabolism and BMD in patients with mild asthma starting inhaled BUD or BDP therapy are now needed to show whether any initial changes occur before systemic corticosteroid therapy is given.

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NUTRITION IN CHILD HEALTH

Edited by D P Davies

Nutrition is fundamental for a child’s normal growth and development and it seems likely that nutrition, even as early as the fetal stage, may be a determinant of adult health. However, despite the great advances in knowledge, doctors as a whole tend to neglect this subject. This timely publication, based on a conference organised by the Royal College of Physicians and the British Paediatric Association, includes an overview of the current state of nutrition in children and adolescents and reflects the many aspects of paediatric nutrition including:

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- The importance of nutrition in the sick and problem child, and how to manage the feeding of children with cerebral palsy and behavioural eating problems
- Proposals for meeting the challenge of malnutrition in developing countries
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This book will be a valuable source of information to paediatricians and other professional workers, particularly dieticians, involved in the care of children, and also to adult clinicians and medical scientists. It provides an up-to-date source of reference for both undergraduate and postgraduate educational and training programmes in childhood nutrition.

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Foreword by Dame June Lloyd  
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◆ Part 2: Nutrition in neonatal care: 5. Human milk: a sacred cow? A quest for optimum nutrition for pre-term babies. 6. The influence of early diet on outcome in pre-term infants. 7. Early nutrition and coronary heart disease. 8. Intra-uterine growth retardation: achieving ‘catch-up’. 9. Nutrition in the sick neonate.  
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