One year prospective open study of the effect of high dose inhaled steroids, fluticasone propionate, and budesonide on bone markers and bone mineral density

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Abstract

***Background*—Inhaled corticosteroids are recognised as the most effective agents in the treatment of asthma. However, concerns have been expressed about the effects of high doses of inhaled corticosteroids on safety in relation to bone resorption and formation. This study measures the effects of two inhaled corticosteroids on bone markers and bone mineral density (BMD) over one year.**

***Methods*—A one year randomised, prospective, open parallel study comparing inhaled fluticasone propionate (FP), 500 µg twice daily in 30 patients, and budesonide (BUD), 800 µg twice daily in 29 patients, delivered by metered dose inhaler and large volume spacers was performed in adults with moderate to severe asthma. Biochemical markers of bone turnover (osteocalcin, procollagen type 1 C-terminal propeptide (PICP), immunoreactive free deoxypyridinoline (iFDpd), N-terminal crosslinked telopeptides of type I collagen (NTx)), BMD at the spine and femoral neck, and serum cortisol concentrations were measured at baseline and 12 months later.**

***Results*—There were no significant differences between the inhaled steroids on bone markers of bone resorption and formation or bone mineral density. Bone mineral density of the spine increased slightly in both groups over the 12 month period. Serum osteocalcin levels increased from baseline in both treatment groups (FP 16.9%, p = 0.02; BUD 14.3%, p = 0.04). PICP did not differ significantly from baseline. Both markers of bone resorption (iFDpd, NTx) varied considerably with no significant changes after one year. There was a significant correlation in percentage change from baseline between BMD of the spine and osteocalcin at 12 months (r = 0.4, p = 0.017). Mean serum cortisol levels remained within the normal range in both groups following treatment.**

***Conclusion*—There was no evidence of a decrease in BMD during 12 months of treatment with high doses of either FP or BUD. The change in spine BMD correlated with the increase in osteocalcin. Studies extending over several years are needed to establish whether these findings persist.**

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Keywords: asthma; inhaled corticosteroids; fluticasone propionate; budesonide; bone markers; bone mineral density

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Inhaled corticosteroids are now recognised as the most effective agents in the treatment of asthma.[1] However, concerns about the safety of high dose inhaled steroids have been expressed.[2–4] Oral corticosteroids are well known to cause osteoporosis[5 6] but whether the long term use of inhaled corticosteroids can affect bone density, leading to osteoporosis, remains controversial. Several authors have identified the need for long term prospective studies to determine whether inhaled corticosteroids affect bone markers and bone density measurements which could then lead to osteoporosis.[1 7]

There have been several studies reporting the effects of inhaled corticosteroids on bone markers[8–18] and bone density[13 14 16 18–24] but these have been largely cross sectional and confounded, in most cases, by previous oral corticosteroid use. Some studies have found normal or near normal bone mineral density (BMD)[14 20 21] while others have reported a reduction in BMD compared with expected values or controls.[13 16 18 22–24]

Fluticasone propionate (FP) is a synthetic glucocorticoid available as an inhaled preparation. It has an oral bioavailability tending towards zero, resulting in virtually no systemic absorption from the swallowed fraction.[25] This may result in there being less effect on BMD or bone markers.

We have therefore compared the effects of high dose inhaled FP (500 µg twice daily) and budesonide (BUD, 800 µg twice daily) in a prospective and randomised study to measure bone markers and BMD over one year. BUD was chosen as a comparison as a previous study with this drug had reported little change in bone markers and BMD.[14]

Methods

PATIENTS

A single centre, open, parallel group study was undertaken. Both FP and BUD were administered with a large volume spacer device and delivered via a metered dose inhaler. Fifty nine patients were randomised using a minimisation procedure according to age (≤35 and >35 years), sex, smoking habits, alcohol consumption (≤21 or >21 units per week for men; ≤14 or >14 units per week for women), level of

Table 1 Demographic data of patients and previous steroid use

	BUD (n = 29)	*FP (n = 30)*
No. of women	10 (34%)	13 (43%)
Menopausal	5 (50%)	7 (54%)
Mean age (range)	56 (25–68)	50 (29–70)
Duration of inhaled steroid use		
<1 year	0	3 (10%)
1–5 years	16 (55%)	12 (40%)
>5 years	13 (45%)	15 (50%)
Use of oral steroids in the past		
No	9 (31%)	5 (17%)
Yes	20 (69%)	28 (83%)
Use of oral steroids during trial		
No	22 (76%)	20 (67%)
Yes	7 (24%)	10 (33%)

FP = fluticasone propionate; BUD = budesonide.

physical activity (light, moderate or heavy) and, for women only, use of the oral contraceptive pill and whether or not post-menopausal. Minimisation is an alternative to randomisation for allocating patients to treatments. In a minimisation routine important prognostic factors are identified before the study (listed above). As subjects become eligible for the study they are allocated to the groups in a way that maintains balance between the groups on each factor. The minimisation routine we used contained a random component to prevent us determining the allocation of a patient in advance. Only patients with moderate or severe asthma aged 21–70 years who were currently stabilised on doses of inhaled corticosteroids equivalent to study medication doses (1.5–2 mg per day beclomethasone dipropionate (BDP) or 1.6 mg per day BUD) were included.

The following exclusion criteria were used: patients taking oral corticosteroids in the preceding three months or more than three short courses (defined as a course which lasted less than three weeks) in the last year; women receiving hormone replacement therapy; patients treated for fractures in the preceding six months and those treated for arthritis or who were suffering from any metabolic bone disease; patients with serious concurrent uncontrolled disease; patients who had received newly prescribed asthma therapy or who had changed their asthma therapy in the eight weeks prior to baseline; and patients with a forced expiratory volume in one second (FEV_1) of <30% predicted normal (table 1).

During the 12 month study any patient who required a short course of oral steroids (defined as being <3 weeks duration) was analysed as an intention to treat group; those not receiving oral steroids were analysed as per protocol. Patients requiring maintenance oral steroids were withdrawn.

Ethical approval was granted by the Tunbridge Wells local research ethics committee which comes under the auspices of the West Kent Health Authority and written consent was obtained from all patients.

STUDY DESIGN

After a two week run in period BMD, bone markers, serum morning cortisol levels, and 24 hour urinary free cortisol levels were measured at baseline, six and 12 months. The BMD measurement, blood and urine samples were taken at the same time of day (±30 minutes) following a 12 hour overnight fast. All assays were performed in duplicate in the same analytical batch. Serum osteocalcin levels were measured by immunoradiometric assay (ELSA-OSTEO, CIS Bio International, Cedex, France, intra-assay coefficient of variation (CV) <5%), serum procollagen type I C-terminal propeptide (PICP) levels by radioimmunoassay (Procollagen PICP, Orion Diagnostica, Esposo, Finland, intra-assay CV <11%), urinary immunoreactive free deoxypyridinolone (iFDpd) levels by enzyme linked immunosorbant assay (ELISA), (Pyrilinks D, Metra Biosytstems Inc, Mountain View, California, USA, intra-assay CV <11%), and urinary N-terminal crosslinked telopeptides of type I collagen (NTx) by ELISA (Osteomark, Ostex, Seattle, WA, USA, intra-assay CV <11%).

Urinary free cortisol levels were measured at the Epsom Hospital laboratories by a competitive protein binding method (CPB). When possible the cortisol concentration obtained was multiplied by the 24 hour urine volume to give the 24 hour urinary free cortisol output. Serum cortisol levels were measured in the laboratories of the Northern General Hospital in Sheffield by radioimmunoassay (Orion Diagnostica, Oulu, Finland) and the intra-assay CV was <7%.

Bone mineral density measurements were performed at the lumbar spine and proximal femur (femoral neck and trochanter) using a Norland XR 26 mark 2 bone densitometer (Norland, Wisconsin, USA) using the 3.0 software program.

Bone density results were expressed as area density in g/cm^2. Precision for in vivo measurements was assessed in 25 normal volunteers aged 20–60. Their paired measurements yielded precision reproducibility of 0.9% for the spine and 2.1% for the femoral neck. Daily quality assurance was performed using the manufacturer's anthropomorphic phantom. These values remained within the manufacturer's recommendations throughout the study period. All examinations were performed by two experienced radiographers. Bone mineral density measurements were reported by the investigators blind as to the patients' treatment allocation.

STATISTICAL METHODS

The percentage change from baseline to 12 months was calculated for all parameters. Treatment groups were compared using the analysis of covariance or the van Elteren test as appropriate to the distribution of the data, adjusting for baseline values. Data were summarised using either means and standard errors or medians and quartiles according to their distribution. Within group tests of the percentage changes from baseline were carried out using the one sample *t* test or Wilcoxon test as appropriate. Analyses were based on the intention to treat sample of patients and repeated on the sample of patients who did not receive oral steroids during the trial.

Table 2 Adverse events leading to withdrawal

Event	*BUD (n=29)*	*FP (n=30)*
Nasal polypectomy	1	0
Poor asthma control	4	0
Allergic reaction	1	1
Headache	0	1
Neoplasm of prostate	0	1
Depression	0	1
Acid indigestion	0	1
Psoriasis	1	0
Neck pain	1	0
Cough/dry mouth	1	0
Failed entry criteria	2	0
Failed to attend	1	0
Non-compliance	0	0
Total	12	5

FP = fluticasone propionate; BUD = budesonide.

Further analyses included comparisons of the groups of patients who had and had not taken oral steroids in the past, and separate comparisons for oral steroid use during the study, again using analysis of covariance or the van Elteren test, adjusting for baseline values. Within group tests of percentage changes from baseline were also carried out for the groups of patients who had and had not taken oral steroids during the study using the one sample *t* test or Wilcoxon test as appropriate.

Correlations between percentage change from baseline in spine BMD and osteocalcin levels, iFDpd and each of the two hip BMD measurements were investigated using Spearman's correlation coefficient, as was the correlation between the percentage changes in the BMD between the hip neck and hip trochanter.

An overall significance level of 5% was taken as evidence of a treatment difference for spine BMD, osteocalcin and iFDpd levels. All other parameters were considered to show statistical evidence of a true treatment difference at the 1% level. 95% confidence intervals for the estimate of true treatment percentage differences were calculated where possible.

The data for patients who withdrew before completing the study were included in the analysis up until the time of withdrawal. All demographic data, baseline clinical information, adverse events, and withdrawal information are presented descriptively.

Table 3 Percentage change per year in bone mineral density (BMD; g/cm^2) from baseline at 12 months (intention to treat sample includes patients given oral steroids during trial)

		FP	*BUD*
Spine	n	25	16
	Mean (SE)	0.49 (0.77)	1.59 (0.90)
	p value (within group)	0.53	0.10
	Difference between means (SE)	1.07 (1.16)	
	95% CI	(−1.28 to 3.43)	
	p value (between groups)	0.36	
Femoral neck	n	25	16
	Median	−1.61	0.15
	Lower quartile	−2.88	−2.09
	Upper quartile	0.23	2.76
	p value (within group)	0.043	1.00
	p value (between groups)	0.043	
Femoral trochanter	n	25	16
	Median	1.77	2.95
	Lower quartile	−0.68	−0.37
	Upper quartile	5.13	5.40
	p value (within group)	0.067	0.21
	p value (between groups)	0.36	

FP = fluticasone propionate 500 μg twice daily; BUD = budesonide 800 μg twice daily; SE = standard error; CI = confidence interval.

As a large number of statistical tests have been performed, the reader should exercise caution in interpreting p values.

Results

Sixty two Caucasian patients were recruited into the study, 59 of whom were randomised to receive either FP (30 patients) or BUD (29 patients) for a treatment period of 12 months. Patient demographic data and steroid use are shown in table 1. Seventeen patients were withdrawn during the treatment period (table 2). As a result of these withdrawals, the number of patients providing 12 months of data was 25 in the FP group and 17 in the BUD group.

In spite of the use of a minimisation procedure to randomise patients, there were a number of baseline differences between treatment groups which may impact on differences observed between the groups. There were proportionately more women in the FP group (52% of those who completed the study compared with 29% of the BUD group) and patients in the FP group were generally younger (median age 48 compared with 58 in the BUD group). The age range, however, was similar for the two treatment groups. The FP group appeared to have patients with more severe asthma as indicated by both past oral corticosteroid use (84% FP and 65% BUD) and baseline lung function (68% predicted peak expiratory flow (PEF) in the FP group compared with 82% for the BUD group).

BONE DENSITY COMPARISONS

BMD values are usually expressed in relation to reference data as standard deviation (SD) scores, a Z score representing the number of SD above or below the age and sex matched reference value; a T score is similarly expressed in relation to the peak reference values for young adults. T scores are preferred when assessing osteopenia and osteoporosis.[29] For both treatment groups almost all had normal T and Z scores at baseline, However, there was one patient in each group with a T score in the osteoporotic range.

SPINE BMD

BMD increased slightly for both treatment groups over the 12 month period, although the increase was not statistically significant in either group (tables 3 and 4). There was no statistically significant difference between the FP and BUD treatment groups. In patients who did not receive oral corticosteroids BMD increased by a mean of 1.5% (p = 0.01) whilst in those who received oral corticosteroids a small mean decrease of 0.24% (p = 0.87) was seen. When the total patient group was divided on the basis of past use of oral steroids there were no apparent differences, with both groups tending to increase their spine BMD slightly over the year of the study.

FEMORAL NECK AND TROCHANTER BMD

There were no differences between the FP and BUD groups except for the measurement of the femoral neck (p = 0.043) which was in favour of BUD. However, when the patients

Table 4 Percentage change per year in bone mineral density (BMD, g/cm²) from baseline at 12 months (per protocol sample, excludes patients who received oral steroids during trial)

		FP	BUD
Spine	n	16	12
	Median	0.51	0.51
	Lower quartile	−0.90	−0.74
	Upper quartile	2.73	4.35
	p value (within group)	0.11	0.059
	p value (between groups)	0.74	
Femoral neck	n	16	12
	Median	−0.95	−0.31
	Lower quartile	−3.11	−2.55
	Upper quartile	0.90	1.86
	p value (within group)	0.20	0.39
	p value (between groups)	0.31	
Femoral trochanter	n	16	12
	Median	2.87	2.65
	Lower quartile	−0.49	−0.57
	Upper quartile	5.18	5.40
	p value (within group)	0.053	0.39
	p value (between groups)	0.15	

FP = fluticasone propionate 500 µg twice daily; BUD = budesonide 800 µg twice daily.

who had received oral corticosteroids during the study were excluded the difference was reduced (p = 0.31). There was no difference observed for either femoral measurement during the 12 month period between those patients who received oral steroids and those who did not. When the patient group was divided on the basis of past use of oral corticosteroids no significant differences were seen.

BONE MARKER COMPARISONS

Markers of bone formation

Osteocalcin levels increased significantly from baseline in both treatment groups (tables 5 and 6). When patients who received oral corticosteroids were excluded the statistical significance increased (p = 0.006) in both treatment groups. There was no difference between treatment groups (p = 0.7). PICP levels did not differ from baseline after 12 months of treatment in either group (tables 5 and 6). Neither osteocalcin nor PICP levels were affected by the use of oral steroids prior to the study.

Table 5 Percentage change in bone markers from baseline at 12 months (intention to treat sample)

		FP	BUD
Osteocalcin (µg/ml)	n	24	17
	Mean (SE)	16.87 (6.03)	14.30 (6.40)
	p value (within group)	0.023	0.04
	Difference between means (SE)	−3.46 (8.81)	
	95% CI	(−21.27 to 14.36)	
	p value (between groups)	0.70	
PICP (µg/l)	n	24	17
	Mean (SE)	1.29 (4.70)	11.16 (8.10)
	p value (within group)	0.79	0.19
	Difference between means (SE)	6.23 (7.69)	
	95% CI	(−9.33 to 21.79)	
	p value (between groups)	0.42	

FP = fluticasone propionate 500 µg twice daily; BUD = budesonide 800 µg twice daily; PICP = procollagen type 1 C-terminal propeptide; SE = standard error; CI = confidence interval.

Table 6 Percentage change in bone markers from baseline at 12 months (per protocol sample, excluding steroid users)

		FP	BUD
Osteocalcin (µg/ml)	n	16	13
	Mean (SE)	15.25 (4.79)	19.07 (5.80)
	p value (within group)	0.0062	0.0065
	Difference between means (SE)	3.03 (7.75)	
	95% CI	(−12.87 to 18.93)	
	p value (between groups)	0.70	
PICP (µg/l)	n	16	13
	Mean (SE)	3.29 (4.79)	3.34 (6.58)
	p value (within group)	0.50	0.62
	Difference between means (SE)	−2.33 (6.97)	
	95% CI	(−16.63 to 11.98)	
	p value (between groups)	0.74	

FP = fluticasone propionate 500 µg twice daily; BUD = budesonide 800 µg twice daily; PICP = procollagen type 1 C-terminal propeptide; SE = standard error; CI = confidence interval.

Markers of bone resorption

Changes in both iFDpd and NTx over the year were variable between patients, with both increases and decreases of over 50%. The mean change in iFDpd in the FP group was a decrease of 1.3% compared with an increase of 8.2% in the BUD group (p = 0.48). Mean NTx levels over the year decreased slightly in both groups (0.39% for FP; 1.6% for BUD) with no difference between groups (p = 0.9). Within treatment groups, comparisons for both iFDpd and NTx indicated that none of the values at 12 months were significantly different from baseline. Bone resorption markers increased in the group of patients not receiving oral steroids during the study period (6% for iFDpd; 2.8% NTx) and decreased in those receiving oral steroids (–5.6% iFDpd; –9.5% NTx). Serum levels of iFDpd and NTx were both unaffected by the use of oral steroids prior to the start of the study.

CORRELATION ANALYSES

A significant correlation was observed between percentage change from baseline per year at 12 months in spine BMD and osteocalcin levels (r = 0.37 (SE 0.16), p = 0.017). No correlation was observed between spine BMD and iFDpd (p = 0.12) nor between spine BMD and either of the two femoral BMD measurements. However, there was a significant correlation (r = 0.45, p = 0.003) between BMD changes in the femoral neck and trochanter at 12 months.

CORTISOL LEVELS

Urinary free cortisol levels

Mean baseline values for both treatment groups were towards the low end of the normal range (normal 25–280 nmol/l) with FP 56.4 nmol/l and BUD 44.0 nmol/l. There was a decrease over the 12 month period in both groups (FP –14.8%; BUD –6.2%) but no difference between groups. A fall in urinary free cortisol levels to below the lower limit of normal occurred in three patients in the BUD group and seven in the FP group, all of whom had normal baseline values. Three of the seven patients in the FP group received oral steroids during the study.

Serum cortisol levels

Mean baseline values were similar for the two treatment groups (FP 298.3 nmol/l, BUD 309.3 nmol/l) and were within the normal range (154–638 nmol/l). Both treatment groups increased slightly during the 12 month study with no difference between treatments. No patients taking BUD and two patients on FP had 12 month values below the normal range.

Discussion

The main aim of the study was to compare the effects of high doses of inhaled FP and BUD given for 12 months on BMD and biochemical

markers in a group of asthmatic patients in which use of such doses of inhaled corticosteroids would be routine.

The primary end point of this study was to compare the effects of two inhaled corticosteroids in high doses. The study did not include a control group of asthmatics receiving no treatment or only bronchodilators. As we were studying moderate to severe asthmatics it was unethical to include such a group who were not taking inhaled steroids. As far as we are aware, bronchodilator use per se has no effect on BMD. To ensure reproducibility the bone densitometer of BMD data was calibrated daily with measurements performed by two experienced radiographers to ensure precision with regard to BMD measurements.

All patients were previously receiving high dose inhaled corticosteroids, mainly in the form of beclomethasone dipropionate (BDP), and many had past exposure to oral corticosteroids. To eliminate where possible the effect of previous oral corticosteroid use, no patients currently receiving or previously having received maintenance oral corticosteroid treatment were included in the study, and patients who had received either one short course of oral corticosteroids in the three months before the start of the study or more than three short courses in the 12 months before the start of the study were also excluded. Fewer subjects than anticipated were recruited into the study. However, a retrospective power calculation suggests that, for the primary parameter of interest (spine BMD), the study had a 90% power to detect a difference between treatments of approximately four percentage points. Finally, the high rate of withdrawal in the BUD group and baseline differences between groups in asthma severity, exercise, and age may impact on any apparent treatment differences.

The results of the study, however, indicate that treatment of moderate/severe asthmatic patients with high dose inhaled corticosteroids (FP 1000 µg daily and BUD 1600 µg daily) is not associated with a decline in BMD measured at either of the lumbar spine, femoral neck or trochanter over a 12 month period. There was, in fact, an increase in bone density over this period for spine and femoral trochanter. The spine BMD was also found to correlate significantly with an increase in the levels of osteocalcin (a marker of bone formation) over this same period. There was no difference between the two inhaled corticosteroids for the primary measures of BMD and markers of bone formation and bone resorption. These findings have important clinical significance, several authors having expressed concern regarding the safety of inhaled corticosteroids given over time.[2–4]

Early studies of the effects of corticosteroids on bone metabolism and the risk of osteoporosis concentrated on bone markers.[9–12 15 17] Although inhaled BUD was shown to decrease osteocalcin levels slightly in healthy volunteers, these changes were small and did not necessarily reflect long term changes.[10 11] Toogood *et al*[12] highlighted possible serious bone complications from the long term use of inhaled corticosteroids; they administered higher doses of inhaled BUD to healthy volunteers for one month and found a significant reduction in osteocalcin at the end of this time. Ali *et al*[9] reported an increase in the hydroxyproline/creatinine ratio after BDP (2000 µg/day) was given to healthy volunteers for a month whereas BUD (1800 µg/day) resulted in no significant changes.

Plasma osteocalcin levels were shown to decrease over one week in healthy volunteers taking 1000 µg BDP daily.[17] In a two part study Kerstjens *et al*[15] found a decrease in osteocalcin levels accompanied by an increase in PICP in 15 patients recently started on at least 800 µg of inhaled corticosteroids daily. No differences were observed in serum levels of PICP in those receiving 800 µg BDP daily and those receiving only bronchodilators before and after a 2.5 year treatment period. However, the relevance of biochemical markers to the development of steroid induced osteoporosis has not been clearly demonstrated.

Bone mass provides the best prediction of fracture risk.[26] Although several techniques are available to measure bone mass, dual energy *x* ray absorptiometry (DXA) is the most widely accepted. It has the advantage over single energy photon and *x* ray absorptiometry in being able to measure bone mass at both axial and appendicular sites. It also has a high reproducibility (1% for spine, 2% for hip)[27] and has a low radiation dose.[28] DXA produces a linear measurement of bone mineral content (g) which can be converted into an area bone density (g/cm^2) by dividing by the area of the scan in the spine and the hip.

The disadvantages of DXA are that measurements of BMD in the spine may be affected by extraskeletal calcium, osteophytes, scoliosis, and vertebral deformity. The distribution of osteoporosis within the spine may be heterogeneous and osteomalacia, if present, may also result in low BMD. It was reassuring therefore to observe that most of the patients included in the study, despite having received inhaled (and, in many cases, oral) corticosteroids, had normal bone density on entry with T scores between +1 and –1.

Previous studies have been criticised for not controlling for oral steroid use.[30] Patients receiving oral steroids during our study showed a small decrease in BMD measurements. However, in those not receiving oral steroids the BMD increased. Contrary to earlier studies of short term changes, there was an increase in osteocalcin levels over 12 months which correlated with the changes in spine BMD.

Packe *et al*[13] reported reduced vertebral bone density in asthmatic patients receiving 1000–2000 µg BDP for one year. However, the effect of previous systemic corticosteroids was not controlled for and may have influenced the results. The same researchers then assessed inhaled BUD (mean daily dose 800 µg) over one year with 13 of the 20 patients having been given systemic steroids previously. This group was compared with 20 patients on high dose BDP (mean daily dose 1000 µg) and no differ-

ence in mean BMD was seen between the two groups.

Hanania *et al*[16] also looked at asthmatic patients taking inhaled BDP or BUD in doses of at least 800 µg daily for a year and compared them with a group who had been taking only bronchodilators. They found a significantly lower osteocalcin level with a reduction in bone density measurements in the group taking inhaled corticosteroids than in the group that had taken only bronchodilators.

Boulet *et al*[14] compared the effects of inhaled BDP in doses of at least 800 µg a day over an 18 month period in 37 asthmatic subjects and in a control group who had taken few or no inhaled corticosteroids (<500 µg/day). They failed to show a significant difference in bone density although there was a significantly lower level of osteocalcin in the group taking higher doses of inhaled corticosteroids.

Herrala *et al*[21] studied the effects of 1000 µg inhaled BDP in asthmatic women and failed to show any significant change in BMD after one year. Marystone *et al*[23] did show a slight reduction in BMD in women using inhaled corticosteroids compared with a group who had never used them. There was no significant difference, however, in men. Ip *et al*[22] also reported a reduction in BMD in a group of female asthmatics but not in male patients although some of these had received unquantified doses of booster systemic steroids. Toogood *et al*[24] measured bone density in 26 men and 43 women, 41 of whom were menopausal, after treatment with both inhaled and oral steroids with a mean duration of treatment with inhaled corticosteroids of 10.1 (5.5) years. They found that bone densities were lower in patients who had taken higher daily doses of inhaled corticosteroids and, not surprisingly, this was associated with the duration of past prednisolone treatment. Interestingly, they found that women with a lifetime dose of inhaled corticosteroids of >3 g had normal bone density regardless of the amount of past or present prednisolone use. They concluded that the daily dose, not the duration of treatment with inhaled steroids, could adversely affect bone density. However, Wolfe *et al*[20] were unable to confirm any significant reduction in bone loss in a small group of asthmatic patients followed for 36–62 months.

Egan *et al*[31] have reported a difference in spine BMD in a group of moderate to severe asthmatic patients taking either FP 1000 µg/day or BDP 2000 µg/day. BMD was measured by quantitative computed tomography (QCT) in a two year prospective randomised study. The BMD of vertebral trabecular bone decreased significantly with BDP but not with FP which showed a slight rise at two years compared with baseline. No changes were seen in mean levels of markers of bone formation/resorption.

Pauwels *et al*[32] in a double blind, multicentre, crossover study of one year duration, compared bone markers and BMD in 167 asthmatic patients taking FP with 173 on BDP. FP treatment resulted in significantly higher osteocalcin levels ($p<0.001$) and higher BMD in the spine ($p = 0.05$), femoral neck ($p<0.01$), and Ward's triangle ($p = 0.01$) compared with BDP.

The increase in BMD and osteocalcin in the present study is perhaps unexpected when the peak bone mass in adults is achieved by the age of 35, the mean age in the two study groups being 50 and 56. Possible reasons for this could be an improvement in asthma control with subsequent increased exercise and a decrease in the need for oral steroid therapy. However, the patients were selected because they were in a stable stage and frequent use of oral steroids and poor control prior to entering the study were reasons for exclusion. Although there was a slight improvement in the mean peak flow readings at six and 12 months compared with baseline in the FP group, this did not reach significance.

Of those entering the study, 76% were receiving BDP; Egan[31] showed a decrease in vertebral trabecular bone density in a group of asthmatic patients taking 2000 µg BDP/day over a two year period. Osteoporosis can be a reversible condition[6 33] and it is possible that switching patients from BDP to BUD or FP allowed bone loss to be restored, resulting in the increase in osteocalcin and BMD measurements. A further possible explanation is that all patients used a large volume spacer device during the study which may have reduced the portion of inhaled steroid that was systemically available from the swallowed fraction,[34] thereby reducing any potential effect on bone metabolism.

In conclusion, there was no evidence of a decrease in bone density during 12 months of treatment with high doses of FP (500 µg twice daily) and BUD (800 µg twice daily). In fact, in patients not receiving short courses of oral steroids there was a significant increase in spine BMD of +1.5% ($p = 0.01$) accompanied by a significant increase in osteocalcin levels.

There was no difference between the treatments to indicate that either BUD or FP delivered by metered dose inhaler and large volume spacer in doses up to those used in this current study have any adverse effects on bone markers or bone density in the medium to long term. Long term follow up of BMD is now required.

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