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Bone turnover during short course prednisolone treatment in patients with chronic obstructive airways disease

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Abstract

Background **Although osteoporosis is a well known side effect of long term prednisolone, the effects of a short course are less clear. Biochemical markers of bone turnover were therefore studied in 10 men with chronic obstructive airways disease who required assessment of "steroid reversibility" (mean age 65 years, mean FEV_1 1·2 l).**

Method **Patients received, single blind, two weeks of placebo, four weeks of prednisolone 20 mg/day, and then two further weeks of placebo.**

Results **The mean (SD) fasting urinary hydroxyproline:creatinine ratio, a marker of bone resorption, increased by 65% with prednisolone (from 8·9 (5·7) to 14·7 (8·5) μmol/mmol) and returned to baseline after placebo. Serum alkaline phosphatase, a marker of net bone formation, fell after prednisolone by 28% (from 113 (41) to 81 (30) IU/l). Substantial changes occurred after only two weeks of prednisolone. Serum osteocalcin, calcium, and phosphate concentrations did not change significantly.**

Conclusions **Short courses of prednisolone increased bone resorption and inhibited bone formation after two and four weeks.**

Cushing's original description of endogenous glucocorticoid excess included an increased tendency for fractures to occur.[1] Since the report of Curtiss *et al*[2] it has become well established that long term oral corticosteroids cause progressive bone loss.[3] Histological studies subsequently showed a substantial increase in bone resorption and a decrease in bone formation.[4,5] Although several studies have found this to be related to the dose of steroid[6,7] a threshold for the effect on bone metabolism is now considered unlikely.[3]

A 2·5% decrease in distal forearm bone mineral content has been shown in the first 12 weeks of prednisone treatment,[8] falling to 0·6% during the second 12 weeks of a subsequent study.[9] Furthermore, dose related annual bone losses of 1–7% in peripheral trabecular bone have been found in asthmatic patients treated with corticosteroids.[6]

Although increases in 24 hour urinary calcium excretion have been reported during the first four weeks of corticosteroid treatment,[10,11] changes in urinary hydroxyproline excretion, an indicator of increased bone resorption, are less well established.[11]

The aim of this study was therefore to investigate bone turnover after two and four weeks of prednisolone in patients with chronic obstructive airways disease who required a "steroid trial" as part of their routine clinical assessment. Bone resorption was assessed biochemically and non-invasively, as in our previous study, by measurement of the fasting urinary hydroxyproline:creatinine ratio and the urinary calcium:creatinine ratio.[12,13] Bone formation was assessed by measurement of serum alkaline phosphatase[13] and serum osteocalcin.[14,15]

Methods

PATIENTS

Ten men (mean age 65, range 56–75 years) were recruited from the outpatient chest clinic. Each had chronic obstructive airways disease, with abnormal values in tests of expiratory flow, which had not changed substantially over several months and which were not related to specific causes of airflow obstruction, as defined by the American Thoracic Society.[16] All but one were previous or current smokers. The mean forced expiratory volume in one second (FEV_1) was 1·2 (range 0·6–2·0) l and in all patients was less than 65% of the predicted value. The mean forced vital capacity (FVC) was 2·2 (range 1·4–3·2) l and the FEV_1/FVC ratio was below 70% in all subjects. All patients were clinically stable.

Patients were excluded if there was any evidence of active bone disease, such as osteoporosis, osteomalacia, Paget's disease, or recent fracture; if they had received oral steroid treatment in the past two months; or if they had any other important medical problems or were taking medication known to alter bone metabolism, such as thiazides or calcitonin.[3]

STUDY DESIGN

This was a single blind, placebo controlled study lasting eight weeks. Placebo was given for two weeks during an initial run in period. Baseline measurements were made at the beginning and end of this period and then all patients were given four weeks of prednisolone, 20 mg daily, during which two further sets of measurements were made after two and four weeks of active treatment. Patients then took

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placebo for a further two week "washout" period, at the end of which the fifth and final set of measurements was made. The tablets were taken as a single daily dose first thing in the morning.

All patients were examined on each of the five visits. An assessment of compliance based on a tablet count was made at each visit and concurrent medication was reviewed. Blood and urine samples were taken between 9.00 and 10.00 am for measurement of biochemical indices of bone turnover. All patients had fasted for 12 hours overnight and had refrained from heavy exertion and alcohol for 24 hours. Having voided urine on first rising, they produced a two hour sample in the clinic. Concentrations of urea, creatinine, calcium, phosphate, electrolytes, glucose, proteins, vitamin D (25-hydroxycholecalciferol), thyroid hormone, and parathyroid hormone were also determined and liver function tests performed.

MEASUREMENTS

Total urinary hydroxyproline was measured by a colorimetric method with an intra-assay precision of 3–10% and an interassay precision of 6–15%.[17] Serum osteocalcin was measured by a commercial immunoradiometric assay (Cis UK) with intra-assay and interassay variability of 5% and 10%. Vitamin D, thyroid hormone, and parathyroid hormone were measured by radioimmunoassay. Calcium, phosphate, creatinine, and alkaline phosphatase were measured by standard methods.

STATISTICS

The baseline for each subject was taken as the mean of the two pretreatment samples. To determine whether the treatment produced a significant effect the area under the curve of the change in each measured variable plotted against time was calculated for individual subjects and tested by the paired *t* test on the assumption that without treatment the baseline would have remained stable—that is, that the area under the baseline would be zero.[18]

The study was approved by the local medical ethics committee and all subjects gave informed written consent.

Results

During prednisolone treatment the mean (SD) urinary hydroxyproline:creatinine ratio rose by 65%, from a baseline of 8·9 (5·7) to 14·7 (8·5) μmol/mmol (table); the area under the curve increased above the baseline by a mean value of 24·5 (18·9) ($p < 0·005$, 95% confidence limits 11·0, 38·0). Most of this increase occurred during the first two weeks. After two weeks of placebo the ratio returned to the baseline value, 9·4 (3·5). The calcium:creatinine ratio rose by 40% from 300 (230) to 420 (230) μmol/mmol; the area under the curve increased above the baseline by a mean value of 390 (780) (NS; 95% confidence limits −170, 950).

Serum alkaline phosphatase (see table) during prednisolone treatment fell by 28% from 113 (41) to 81 [30] IU/l and the area under the curve decreased below baseline by a mean value of 110 (71) ($p < 0·001$, 95% confidence limits 59, 161). Most of this decrease occurred during the first two weeks. Serum osteocalcin did not change significantly (3·3 (1·6) to 3·3 (1·9) μg/l), nor did the area under the curve (− 0·4 (13·5); NS, 95% confidence limits − 10·0, 9·2).

There were no significant changes in urea, creatinine, calcium, phosphate, electrolytes, glucose, proteins, or liver function. All 10 patients had normal thyroid function and vitamin D concentrations. In one baseline calcium and parathyroid hormone concentrations were modestly increased (2·73 mmol/l and 8·5 pmol/l).

Discussion

In this study substantial increases in the fasting urinary hydroxyproline:creatinine ratio occurred during two to four weeks' treatment with prednisolone 20 mg daily. This ratio is a well validated marker of bone resorption and correlates highly with both kinetic and histological indicators of total bone resorption.[13 14] An increased ratio usually reflects high bone turnover, as in Paget's disease of bone, perimenopausal bone loss, or hyperparathyroidism.[13 14]

Gennari found a 77% increase in the total hydroxyproline:creatinine ratio after 30 days of prednisone 20 mg but only a 30% increase after deflazocort 30 mg; the calcium:creatinine ratio rose by 73% and 29%.[11] No change in the hydroxyproline:creatinine ratio was seen in nine normal subjects after only five days' prednisone 20 mg twice daily,[19] but we are not aware of studies of longer duration in normal subjects. After two and four weeks' prednisolone treatment, however, a substantial rise in the hydroxyproline:creatinine ratio was seen in our patients. Ali *et al* found a 46% increase in the hydroxyproline:creatinine ratio after four weeks of inhaled beclomethasone dipropionate 2000μg daily in normal men and a small but significant fall in serum alkaline phosphatase of 7·4%. Substantial changes had likewise occurred after only two weeks.[12] Toogood *et al* found

Mean (SD) values for biochemical markers of bone metabolism before, during, and after prednisolone treatment

	Baseline	*Two weeks' prednisolone*	*Four weeks' prednisolone*	*Placebo*
Hydroxyproline:creatinine ratio (μmol/mmol)	8·9 (5·7)	14·6 (9·8)	14·7 (8·5)	9·4 (3·5)
Calcium:creatinine ratio (μmol/mmol)	300 (230)	420 (140)	420 (230)	260 (150)
Alkaline phosphatase (IU/l)	113 (41)	89 (31)	81 (30)	113 (40)
Osteocalcin (μg/l)	3·3 (1·6)	3·2 (1·5)	3·3 (1·9)	4·5 (1·6)

a reduction in the fasting urinary calcium: creatinine ratio in 10 normal adults given inhaled budesonide 2·4 mg daily for seven days but did not measure hydroxyproline.[20] We can therefore confirm that short courses of prednisolone produce substantial resorption of bone. Several mechanisms may play a part, including a reduction in the proliferation of osteoblast precursors and osteoblast activity and increases in the activity of osteoclasts, the secretion of parathyroid hormone, and the sensitivity of the skeleton to vitamin D3; the absorption of calcium and phosphate by the gut and reabsorption by the kidney are also reduced.[3 21 22]

Serum alkaline phosphatase fell after two and four weeks of prednisolone, indicating a reduction in net bone formation, without changes in serum calcium or phosphate. Serum osteocalcin concentrations were about half the normal in cross sectional studies of asthmatic patients receiving long term glucocorticoid treatment.[23 24] In normal subjects given 40 mg prednisone for five days osteocalcin fell by 75%.[19] The lack of change in osteocalcin in our patients was therefore unexpected, but may have reflected their relatively low concentrations before they started taking prednisolone.

Short courses of corticosteroids used in the assessment or treatment of airflow obstruction therefore increase bone resorption and inhibit bone formation and may contribute to long term loss of bone mass. This may be particularly relevant in women already at risk of osteoporosis. Furthermore, such short courses may contribute to the reduction in total body calcium observed in asthmatic patients taking low dose inhaled corticosteroids.[25 26]

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