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

D Morrison, N J Ali, P A Routledge, S Capewell

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 FEV₁, 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. Since the report of Curtiss et al it has become well established that long term oral corticosteroids cause progressive bone loss. Histological studies subsequently showed a substantial increase in bone resorption and a decrease in bone formation. Although several studies have found this to be related to the dose of steroid a threshold for the effect on bone metabolism is now considered unlikely.

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

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

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. Bone formation was assessed by measurement of serum alkaline phosphatase and serum osteocalcin.

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. All but one were previous or current smokers. The mean forced expiratory volume in one second (FEV₁) 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 FEV₁/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.

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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Methods

Results

Discussion

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

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Two weeks’ prednisolone</th>
<th>Four weeks’ prednisolone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyproline:creatinine (µmol/mmol)</td>
<td>8.9 (5.7)</td>
<td>14.6 (9.8)</td>
<td>14.7 (8.5)</td>
<td>9.4 (3.5)</td>
</tr>
<tr>
<td>Calcium:creatinine (µmol/mmol)</td>
<td>300 (230)</td>
<td>420 (140)</td>
<td>420 (230)</td>
<td>260 (150)</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/l)</td>
<td>113 (41)</td>
<td>89 (31)</td>
<td>81 (30)</td>
<td>113 (40)</td>
</tr>
<tr>
<td>Osteocalcin (µg/l)</td>
<td>3.3 (1.6)</td>
<td>3.2 (1.5)</td>
<td>3.3 (1.9)</td>
<td>4.5 (1.6)</td>
</tr>
</tbody>
</table>

Mean (SD) values for biochemical markers of bone metabolism before, during, and after prednisolone treatment.
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.23 24

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.25 26 In normal subjects given 40 mg prednisolone 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.20 26

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26 Crompton GK. Corticosteroids and bone mass in asthma. BMJ 1987;294:123.
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