Comparative review of the effects of inhaled beclomethasone dipropionate and budesonide on bone

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Introduction

The role of inflammation in asthma is now well recognized, and corticosteroids are being used increasingly in its treatment. However, frequent high-dose courses of oral steroids result in many side-effects including loss of bone mass, which can eventually lead to osteoporosis and fractures (1). Several mechanisms may be involved in this process (2–5) (Fig. 1). Inhaled steroids have a wider therapeutic margin than oral steroids as a result of their high topical: systemic potency ratio, low bioavailability and high systemic clearance (2). It is now recommended that regular inhaled steroids are started earlier in the course of asthma and that high doses are used initially to attain control of the disease (6), but there is still some concern that the amount absorbed might be sufficient to cause systemic side-effects.

The effect of high-dose inhaled corticosteroids on bone has been investigated in healthy adult volunteers and asthma patients of various ages. This review summarizes the data on beclomethasone dipropionate (BDP) and budesonide, the two most widely used inhaled steroids in the U.K.

Experience in Adults

HEALTHY VOLUNTEERS

Non-comparative studies

Studies in healthy adult volunteers have investigated the effects of high-dose inhaled corticosteroids on bone turnover using serum and urinary levels of various markers of bone metabolism, including hormones, enzymes and bone constituents. Non-comparative and placebo-controlled studies in subjects receiving high-dose BDP or budesonide for periods of 1 week to 1 month have generally found a reduction in serum osteocalcin levels, which has been interpreted as indicating reduced bone formation by osteoblasts (Table 1) (7–15). This reduction is reversible; levels have been shown to return to baseline within 1 week of ceasing treatment with BDP 2000 pg daily (13). A placebo-controlled, cross-over study in 16 volunteers receiving BDP 400–2000 µg daily for 10 days attempted to define the threshold dose at which bone is affected (14). A dose-dependent fall in serum osteocalcin levels was observed with BDP doses up to 1400 µg daily, at which the response reached a plateau. A study comparing oral prednisolone 15 mg daily with inhaled BDP 1000 µg daily reported a decrease in serum osteocalcin with both treatments, but the decrease was greater in volunteers receiving prednisolone (10). In contrast, Peretz and Bourboux (12) detected no significant changes in serum osteocalcin, or any of the biochemical markers measured, in volunteers receiving inhaled BDP 1000 µg daily for 1 week.

Toogood et al. (15) found that inhaled budesonide 1200 or 2400 µg daily for 1 month reduced serum osteocalcin levels but did not alter urinary calcium or hydroxyproline output. Two further randomized, double-blind studies comparing the effects of inhaled budesonide and oral prednisolone reported similar results. In the first study (8,9), increasing doses of budesonide or prednisolone over a period of 3 weeks caused significant reductions in serum osteocalcin levels, but other serum and urinary markers remained unchanged. In the second study (7), 40 subjects received either high- or low-dose oral prednisolone or inhaled budesonide for 2 weeks while 10 control subjects received placebo. Serum osteocalcin levels were significantly reduced from baseline in a dose-dependent manner during the first week of steroid therapy in both treatment arms, with there being no significant difference between treatments. No effect on urinary calcium or hydroxyproline was seen during
bone constituents following decreased bone formation or increased resorption

Increased osteoclast activity leading to increased bone resorption.

Effects most apparent in trabecular bone (vertebrae, femoral neck)

FIG. 1. Possible mechanisms by which oral steroids may cause bone loss.

budesonide treatment, in contrast to increases in these parameters with high-dose prednisolone.

Nadeau et al. (11) found no effects of budesonide (at doses up to 2400 µg daily for 14 days) on intestinal calcium absorption, serum calcium, phosphate and PTH levels.

Comparative studies

Four studies have directly compared the effects of BDP and budesonide on bone metabolism in healthy volunteers, and these are summarized in Table 2 (16–19). Brown et al. (17) measured plasma osteocalcin following inhalation of BDP or budesonide 2000 µg daily from metered dose inhalers (MDIs) with or without a spacer on six separate study days. There were no significant changes in plasma osteocalcin following budesonide, with or without a spacer; BDP reduced plasma osteocalcin at 24 h when inhaled without a spacer, but not when a spacer was used. In contrast, in another study BDP 2000 µg daily for 4 weeks via an MDI plus spacer produced a statistically significant increase in the urinary hydroxyproline:creatinine ratio and a fall in serum alkaline phosphatase (16). However, values for both of these parameters remained within the normal ranges during treatment, and hence the clinical significance of these changes is uncertain. In addition, this study also found that in healthy volunteers inhaling budesonide 1800 µg daily through a spacer for 4 weeks there were no significant changes for any of these markers (16).

Nadeau et al. (11) received each treatment for 1 week at the lower dose and then 1 week at the higher dose (19). At the lower doses, neither drug had an appreciable effect on serum osteocalcin. However, BDP 2000 µg daily produced a significant reduction in serum osteocalcin levels, which was not observed after budesonide 1600 µg daily.

The results of all volunteer studies in healthy volunteers indicate that both high-dose inhaled BDP and budesonide can impair bone metabolism but that inhaled steroids, even when used at very high doses, have considerably less effect than oral steroids. In addition, budesonide appears to have less effect than BDP on bone turnover indices (particularly osteocalcin) at clinically relevant doses. However, these results have to be interpreted with caution as the response to steroids in healthy subjects may be different from that in asthma patients, and asthma itself may have an effect on bone metabolism. Effects on bone in asthma patients are therefore difficult to predict from volunteer studies. In addition, all these studies used small subject groups that lacked statistical power, while several were uncontrolled (10,11,13) and/or included doses higher than those used in clinical practice (7–9,11,15). One study included patients in both treatment arms without a formal cross-over design, which might have confounded the results (16). Furthermore, all of these studies examined the effects of the two steroids on bone metabolism for periods of less than 1 month. Such short-term effects may be at least partially compensated over time and do not necessarily translate into osteoporosis in the long term (20). A further problem was that no absolute baseline values were given in some studies (14,18) and it is difficult to assess, therefore, whether the statistically significant changes found are of clinical relevance.

ASTHMA PATIENTS

Studies in asthma patients have investigated the effects of high-dose inhaled corticosteroids on bone density and bone turnover (Tables 3 and 4) (11–25).
<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of subjects</th>
<th>Study design</th>
<th>Duration of therapy (weeks)</th>
<th>Daily dosage of treatment</th>
<th>Overall results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodsman et al. (7) (F)</td>
<td>50</td>
<td>r, db, pg, pc</td>
<td>2</td>
<td>Budesonide 800 µg&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Dose-related reduction in serum osteocalcin (PRED = BUD). No effect on urinary Ca or hydroxyproline with budesonide.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Budesonide 3200 µg&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Prednisolone 10 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prednisolone 40 mg</td>
<td>Prednisolone 800, 1600 and 3200 µg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prednisolone 5, 10 and 20 mg</td>
</tr>
<tr>
<td>Jennings et al. (8, 9) (F, F)</td>
<td>12</td>
<td>r, db, co</td>
<td>3 (1 week at each dose level)</td>
<td>Oral prednisolone 15 mg</td>
<td>Decreased osteocalcin in both groups (PRED &gt; BUD). No effect on serum AP, serum and urinary Ca, or urinary hydroxyproline.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BDP 1000 µg</td>
<td>Decreased osteocalcin in both groups. PRED &gt; BDP. No effect on intestinal Ca absorption, serum Ca and phosphate, or serum PTH.</td>
</tr>
<tr>
<td>Meeran et al. (10) (A)</td>
<td>30</td>
<td>o</td>
<td>1</td>
<td>Budesonide 600–2400 µg&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Prednisolone 5, 10 and 20 mg</td>
</tr>
<tr>
<td>Nadeau et al. (11) (A)</td>
<td>10</td>
<td>o</td>
<td>2</td>
<td>BDP 1000 µg</td>
<td>No effect on serum osteocalcin, AP or PTH, urinary Ca or urinary hydroxyproline.</td>
</tr>
<tr>
<td>Peretz and Bourboux (12)</td>
<td>10</td>
<td>pc</td>
<td>1</td>
<td>BDP 1000 µg</td>
<td>No effect on urinary hydroxyproline. Reversible fall in osteocalcin levels. Significant fall on days 8 and 15, returned to baseline by day 22.</td>
</tr>
<tr>
<td>Pouw et al. (13) (F)</td>
<td>8</td>
<td>o</td>
<td>2</td>
<td>BDP 2000 µg</td>
<td>Levels on days 8 and 15 were identical. Dose-dependent fall in serum osteocalcin levels relative to placebo; plateau above 1400 µg day&lt;sup&gt;–1&lt;/sup&gt;. No absolute values quoted.</td>
</tr>
<tr>
<td>Teelucksingh et al. (14)</td>
<td>16</td>
<td>r, db, pc, co</td>
<td>10 days</td>
<td>BDP 400, 800, 1400 and 2000 µg</td>
<td>Serum osteocalcin fell with both doses of budesonide. No effect on urinary Ca or hydroxyproline.</td>
</tr>
<tr>
<td>Toogood et al. (15) (F)</td>
<td>48</td>
<td>r, co, db, pc, pg</td>
<td>1 month</td>
<td>Budesonide 1200 and 2400 µg</td>
<td></td>
</tr>
</tbody>
</table>

A, abstract; AP, alkaline phosphatase; Ca, calcium; co, cross-over; db, double blind; F, full paper; o, open; pc, placebo controlled; pg, parallel group; PTH, parathyroid hormone; r, randomized.

<sup>a</sup> Number of subjects who completed the trial.

<sup>b</sup> Duration of treatment with each active treatment.

<sup>c</sup> PRED>BUD denotes that prednisolone had a significantly greater effect on bone than budesonide; PRED>BDP indicates that prednisolone had a significantly greater effect on bone than BDP.

<sup>d</sup> Administered with a spacer.
<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Study design</th>
<th>Duration of therapy&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Daily dosage of treatment</th>
<th>Overall results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ali et al. (16) (F)</td>
<td>12</td>
<td>o</td>
<td>4</td>
<td>BDP 2000 µg&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Significantly greater effects on hydroxyproline and AP with BDP but all values within the normal clinical range.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Budesonide 1800 µg&lt;sup&gt;c&lt;/sup&gt;</td>
<td>BDP without a spacer reduced plasma osteocalcin at 24 h. Use of a spacer prevented this effect. No effect with budesonide.</td>
</tr>
<tr>
<td>Brown et al. (17) (F)</td>
<td>9</td>
<td>r, db, co</td>
<td>6 separate days</td>
<td>BDP 2000 µg&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Significantly greater fall in serum osteocalcin and AP, and significantly greater increase in the urinary creatinine:hydroxyproline ratio with BDP. Both drugs increased serum phosphate.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Budesonide 2000 µg&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Study in premenopausal women. BDP 200 µg day&lt;sup&gt;-1&lt;/sup&gt; caused a significant fall in serum osteocalcin</td>
</tr>
<tr>
<td>Jennings et al. (18) (F)</td>
<td>39</td>
<td>co</td>
<td>4</td>
<td>BDP 800 and 2500 µg</td>
<td>BDP 1000 µg day&lt;sup&gt;-1&lt;/sup&gt; and budesonide had no effect.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Budesonide 800 and 2500 µg</td>
<td></td>
</tr>
<tr>
<td>Leech et al. (19) (F)</td>
<td>21</td>
<td>r, db, pc</td>
<td>1 week at each dose</td>
<td>BDP 1000 and 2000 µg</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Budesonide 800 and 1600 µg</td>
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</table>

AP, alkaline phosphatase; co, cross-over; db, double blind; F, full paper; o, open; pc, placebo controlled; r, randomized.

<sup>a</sup> Number of patients who completed the trial.

<sup>b</sup> Duration of treatment with each active treatment.

<sup>c</sup> Administered with a spacer.

<sup>d</sup> Administered with and without a spacer.
Non-comparative studies

Kerstjens et al. (23) retrospectively analysed samples from a randomized, double-blind, parallel-group study in which patients on bronchodilators received additional BDP (800 μg daily), ipratropium bromide or placebo. No significant differences in levels of PICP, a marker of bone formation, or ICTP, an indicator of resorption, were detected between serum samples collected before and after 2-5 yr of treatment in the BDP-treated group.

Boulet et al. (21) compared the effects of high-dose BDP or budesonide (≥800 μg daily) taken for at least 18 months with those of low doses (<500 μg daily) in matched groups of patients with low oral steroid usage over the previous 2 yr. Serum osteocalcin was lower and urinary phosphate higher in patients using high-dose inhaled steroids, but there were no significant differences in the bone density of the lumbar spine and hip or markers of bone metabolism between low- and high-dose groups. In addition, there were no significant differences in bone density or osteocalcin levels between patients receiving BDP and budesonide, although this study was not designed to compare differences between the individual agents. A further study in patients who had taken a mean dose of 1323 μg daily of BDP or budesonide for a median of 2 yr also found significantly reduced osteocalcin levels compared with age- and sex-matched patients receiving bronchodilators only (22). The mean density of the femoral neck of these patients was significantly reduced in the steroid-treated group and was below the normal clinical range; however, there was no significant difference in this parameter between steroid-treated patients and those receiving bronchodilators alone, possibly suggesting it might be disease related. Mean bone density in the lumbar spine and Ward's triangle of the femur remained within the expected clinical range in both treatment groups.

Four studies have reported the effects of oral and inhaled steroids on bone turnover and density. Luengo et al. (24) observed no differences in calcium absorption or PTH serum levels between steroid-dependent patients treated with inhaled BDP (400–1600 μg daily) or oral steroids for a mean of 6-7 yr, and age- and sex-matched healthy volunteers. In a second study, Luengo et al. (25) compared changes in bone mass over 2 yr in 21 patients on oral steroids (mean 12 mg daily), 21 on inhaled BDP (100–900 μg daily), and 875 control subjects. The rate of bone loss for patients on oral steroids was higher than in control subjects, whereas there was no difference in this parameter between those on inhaled steroids and controls. Wolff et al. (28) reported a dose–response relationship between cumulative oral steroid dose and bone loss in five patients receiving an average of 12.5 mg daily oral prednisolone or equivalent for 1–10 yr, but there was no evidence of reduced bone density in five patients who had received inhaled steroids (average dose 326 μg daily BDP or equivalent) for a similar period. Packe et al. (26) compared 17 patients with mild asthma who were steroid naive, 20 on inhaled BDP (1000–2000 μg daily for >1 yr) and 20 on inhaled steroids plus continuous low-dose oral steroids. Bone densities were significantly reduced with both oral and inhaled therapy, but the levels of markers of bone turnover in serum and urine remained unchanged.

Packe et al. (26) measured trabecular BVD in patients who had received inhaled budesonide (median dose 800 μg daily) for >1 yr. BVD values for these patients were compared, retrospectively, with those from patients of an earlier study (26) who had used BDP (median dosage 1000 μg daily) for >1 yr and patients who were steroid naive. Budesonide and BDP patients were matched for age, level of activity and asthma severity. BVD was significantly lower in both the budesonide and the BDP groups than in untreated patients. There was no significant difference in BVD between the BDP and budesonide patients, even when the budesonide results were adjusted to take into account the significant difference in dosage. Moreover, no significant differences in serum or urinary markers of bone turnover were observed between the three groups.

Comparative studies

In a pilot study to validate two novel markers of bone turnover, Kerstjens et al. (23) measured serum alkaline phosphatase, osteocalcin and PICP levels as markers of bone formation, together with the urinary hydroxyproline:creatinine ratio and serum ICTP levels as markers of bone resorption, in patients receiving budesonide or BDP 2800 μg daily. In both treatment groups osteocalcin levels decreased significantly while PICP levels and the PICP:ICTP ratio increased significantly after 4 weeks of treatment. There were no significant differences in serum osteocalcin, PICP or ICTP between groups receiving budesonide or BDP. Morrison et al. (29) detected no changes in the urinary hydroxyproline:creatinine or calcium:creatinine ratios or serum alkaline phosphatase in patients with chronic obstructive airways disease treated with BDP or budesonide 2000 μg daily in a placebo-controlled cross-over trial. However, significant reductions were observed in both treatment groups in the urinary pyridinoline:creatinine and deoxypyridinoline:creatinine ratios, indicating reduced bone resorption. Serum osteocalcin levels fell by 26% with budesonide and 18% with BDP but, because a significant period effect was apparent and baseline osteocalcin levels were significantly different between treatments, there is no significant difference between the two steroids.
<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Study design</th>
<th>Treatment duration</th>
<th>Daily dosage of treatment</th>
<th>Overall results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boulet et al. (21) (F)</td>
<td>74</td>
<td>cs, c</td>
<td>&gt; 18 months (mean 34 months)</td>
<td>BDP or budesonide ≥800 µg BDP or budesonide ≤ 500 µg</td>
<td>Serum osteocalcin reduced, urinary phosphorus increased with high dose BDP and budesonide. No effect on bone density, serum creatinine, Ca, phosphate and AP, or urinary creatinine, Ca and hydroxyproline.</td>
</tr>
</tbody>
</table>
| Hanania et al. (22) (F) | 36              | cs, pg, c    | Median 2 yr        | BDP or budesonide, mean 1323 µg Bronchodilators only | Significant fall in serum osteocalcin in ICS group. Significant fall in bone density in femoral neck from baseline in ICS group, but difference between groups not significant. Bone density in lumbar spine and Ward's triangle of femur not altered.
<p>| Kerstjens et al. (23) (F) | 70              | retro, r, db, pg | 2-5 yr            | Bronchodilators ± BDP 800 µg lpratropium bromide BDP 400-1200 µg Oral steroids | No differences in PICP or ICTP levels with BDP. Asthma patients were steroid dependent. No difference in Ca absorption or PTH serum levels between asthma patients and healthy subjects. |
| Luengo et al. (24) (F) | 50              | cs, c        | Mean 6-7 yr        | OCS mean dose 12 mg BDP 100-900 µg | Decreased bone mass in OCS group. No effect in ICS group. Bone density reduced in both OCS + BDP and BDP groups. Serum Ca, AP and osteocalcin, and urinary pyridinium cross-link levels, unchanged. |
| Luengo et al. (25) (A) | 42              | cs           | 2 yr               | BDP 1000-2000 µg         |                                                                         |
| Packe et al. (26) (F)  | 57              | cs           | &gt; 1 yr             | OCS + BDP                |                                                                         |</p>
<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients(^a)</th>
<th>Study design</th>
<th>Treatment duration(^b)</th>
<th>Daily dosage of treatment</th>
<th>Overall results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packe et al. (27) (F)</td>
<td>20</td>
<td>retro, cs</td>
<td>&gt; 1 yr</td>
<td>Budesonide median dose 800 μg BDP median dose 1000 μg</td>
<td>VBD lower in ICS patients than in steroid-naive controls. VBD in BDP patients = VBD in budesonide patients. No differences in serum AP and osteocalcin or urinary pyridinium cross-links between any group. All BDP patients and 13/20 budesonide patients had received OCS. No budesonide patients had received BDP.</td>
</tr>
<tr>
<td>Wolff et al. (28) (F)</td>
<td>10</td>
<td>cs</td>
<td>1–10 yr</td>
<td>ICS mean dose 326 μg OCS mean dose 12.5 mg</td>
<td>Bone density normal in ICS group but decreased in OCS group.</td>
</tr>
</tbody>
</table>

\(A\), abstract; AP, alkaline phosphatase; c, controlled; Ca, calcium; cs, cross-sectional; db, double blind; F, full paper; ICS, inhaled corticosteroid; ICTP, type I collagen carboxy-terminal telopeptide; OCS, oral corticosteroid; PICP, procollagen type I carboxy-terminal propeptide; pg, parallel group; r, randomized; retro, retrospective; VBD, vertebral bone mineral density; yr, year.

\(^a\) Number of patients who completed the trial.

\(^b\) Duration of treatment with each active treatment.
<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Study design</th>
<th>Treatment duration&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Daily dosage of treatment</th>
<th>Overall results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kerstjens et al. (23) (F)</td>
<td>15</td>
<td>o</td>
<td>4 weeks</td>
<td>BDP ≥800 μg, Budesonide ≥800 μg</td>
<td>Osteocalcin levels decreased. No difference between BDP and budesonide effects on osteocalcin, PICP or ICTP. Significant reduction in urinary pyridinoline:creatinine and deoxypyridinoline: creatinine ratios. Serum osteocalcin significantly reduced by budesonide and BDP, but no difference between drugs. No change in urinary hydroxyproline:creatinine or Ca:creatinine ratios.</td>
</tr>
<tr>
<td>Morrison et al. (29) (A)</td>
<td>10</td>
<td>pc, co</td>
<td>4 weeks each; treatment periods separated by 2 week run-in and wash-out periods</td>
<td>BDP 2000 μg, Budesonide 2000 μg</td>
<td></td>
</tr>
</tbody>
</table>

A, abstract; Ca, calcium; cc, cross-over; F, full paper; ICTP, type 1 collagen carboxy-terminal telopeptide; o, open; OCS, oral corticosteroids; pc: placebo controlled; PICP, procollagen type I carboxy-terminal propeptide.

<sup>a</sup> Number of patients who completed the trial.

<sup>b</sup> Duration of treatment with each active treatment.
These studies in asthma patients generally confirmed the effects of inhaled corticosteroids on markers of bone turnover observed in healthy volunteers. However, bone density studies, although conducted using accurate, modern techniques, show conflicting results. While these studies were conducted over longer periods of time, in larger groups of patients and at more clinically relevant doses than the volunteer studies, many were retrospective or cross-sectional and could not evaluate progressive changes over time. In addition, most patients had previously taken oral corticosteroids, and the possible impact of this on bone could not be assessed.

POST-MENOPAUSAL WOMEN
Loss of bone mass occurs as a natural consequence of ageing. It may begin as early as the third decade in women and accelerates after the menopause when the protective effect of oestrogen is lost (30,31). Hence, any additional bone loss caused by corticosteroid treatment is an obvious cause for concern in this group of patients already at increased risk of osteoporosis.

Puolijoki et al. (32) assessed bone metabolism in nine post-menopausal women with asthma receiving BDP 200, 1000 or 2000 µg daily via a spacer for 3 weeks. Serum osteocalcin was significantly reduced throughout the 9-week follow-up period, but there were no significant alterations in other serum or urinary markers of bone turnover (Table 5). Stead et al. (32) investigated bone mineral density in a cross-sectional study in 11 asthmatic women aged 36–73 years, most of whom were post-menopausal. Ten had received BDP or budesonide 750–2000 µg daily for 1–10 yr, and one had received both drugs. Lumbar spine bone density was reduced by 13% in these patients compared with healthy age-matched controls, but there was no evidence of active, rapid bone loss (Table 5). It is possible that previous oral corticosteroid therapy may have played a role in reducing bone mass in these patients.

Experience in Children
The impact of inhaled corticosteroids on bone formation is a particularly important aspect of treatment in children since they are actively growing. Studies in the patient population are summarized in Table 5 (34–38).

Two studies reported no significant differences in bone mineralization or density between asthmatic children receiving BDP 300–800 µg daily for 6–25 months and age-matched controls (34,37); serum osteocalcin was also unaffected (37). Priftis et al. (38) studied the effect of long-term use of inhaled BDP on biochemical markers of bone turnover and bone mineral content in 33 asthmatic children (median age 10 years) treated with BDP 180–790 µg m⁻² day⁻¹ for 6–48 (mean 11.5) months. A dose-dependent, but not time-dependent, decrease in serum osteocalcin was demonstrated and the urinary calcium:creatinine ratio was elevated. No effects on markers of bone resorption were observed, but there was a reduction in bone mineralization that was independent of both dose and time.

Doull et al. (36) found no significant differences in baseline or three-monthly serum osteocalcin and urinary hydroxyproline measurements in 94 children receiving either BDP 200 µg twice daily by dry powder inhalation or placebo for 6 months in a randomized, double-blind trial. In contrast, an open, cross-over study during which 13 pre-pubertal children received BDP 800 µg daily via a Diskhaler® and budesonide 800 µg daily via a Turboshaker® for 14 days found significantly reduced levels of PICP, the amino terminal of type III collagen, together with decreased urinary pyridinoline and deoxypyridinoline cross-links; this indicates suppression of bone and collagen turnover. This suppression was more apparent with BDP. Osteocalcin levels were not affected by either treatment (35).

These results suggest that continuous treatment with BDP ≤800 µg daily does not affect bone density in children. A reduction in bone and collagen turnover observed was with both budesonide and BDP at these doses, with the effect of budesonide being slightly less than that of BDP.

Considerations
The threshold dose at which systemic side-effects appear with inhaled BDP in adults is believed to be approximately 1000 µg daily (39). However, results have varied considerably between studies, with some studies in adults reporting no effects on bone turnover indices or bone mass with BDP ≤1000 µg daily (12,19,23–25), while others found effects on osteocalcin at BDP doses of ≤1000 µg daily (10,14) or budesonide doses of 800–1200 µg daily (7–9,15). Thus, the threshold dose for the effects of inhaled steroids on bone cannot clearly be defined.

The difference in effects on markers of bone turnover may reflect the sensitivities of these indicators. Osteocalcin is a bone matrix protein that is released by osteoblasts and widely regarded as a sensitive marker of bone formation. However, it can also be released during resorption (40) and attracts osteoclasts (41). The clinical significance of osteocalcin suppression remains unknown and it may be most useful when used in conjunction with other markers. Changes in levels of collagen-related proteins, such as PICP and ICTP, mirror those of osteocalcin (23), but collagen is
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<tr>
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<th>Treatment duration</th>
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<tr>
<td>Puolijoki et al. (32) (A)</td>
<td>9</td>
<td>o</td>
<td>Post-menopausal women</td>
<td>3 weeks</td>
<td>BDP 200, 1000 and 2000 µg</td>
<td>Significant fall in osteocalcin. No change in serum PTH, calcitonin and AP or urinary Ca and hydroxyproline.</td>
</tr>
<tr>
<td>Stead et al. (33) (A)</td>
<td>11</td>
<td>cs</td>
<td>Women aged 36-73 years; most post-menopausal</td>
<td>1-10 yr</td>
<td>BDP 750-2000 µg, Budesonide 800-1600 µg</td>
<td>No evidence of rapid bone loss.</td>
</tr>
<tr>
<td>Baraldi et al. (34) (F)</td>
<td>30</td>
<td>cs, c</td>
<td>Children, mean age 9 years</td>
<td>6 months</td>
<td>BDP 300-400 µg</td>
<td>No effect on bone mineral density. Significant fall in PICP, PIIINP, and urinary pyridinoline and deoxypyridinoline cross links in both groups. No difference between treatments. No difference in serum osteocalcin or urinary hydroxyproline between groups. No effect on bone mineralization or serum osteocalcin with BDP. Dose-dependent fall in serum osteocalcin. No effect on bone resorption.</td>
</tr>
<tr>
<td>Birkbaek et al. (35) (F)</td>
<td>13</td>
<td>o, co</td>
<td>Pre-pubertal children, mean age 8-7 years</td>
<td>14 day treatment periods separated by 14 day run-in and wash-out periods</td>
<td>BDP 800 µg via Diskhaler, Budesonide 800 µg via Turbuhaler</td>
<td></td>
</tr>
<tr>
<td>Doull et al. (36) (A)</td>
<td>94</td>
<td>r, db, pc</td>
<td>Children</td>
<td>6 months</td>
<td>BDP 400 µg</td>
<td></td>
</tr>
<tr>
<td>Konig et al. (37) (A)</td>
<td>18</td>
<td>cs, c</td>
<td>Children, mean age 10 years</td>
<td>Mean 25 months</td>
<td>BDP 300-800 µg</td>
<td></td>
</tr>
<tr>
<td>Priftis et al. (38) (A)</td>
<td>33</td>
<td>cs</td>
<td>Children, median age 10 years</td>
<td>6-48 months (mean 11.5 months)</td>
<td>BDP 180-790 µg m²</td>
<td></td>
</tr>
</tbody>
</table>

A, abstract; AP, alkaline phosphatase; c, controlled; Ca, calcium; co, cross-over; cs, cross-sectional; db, double blind; F, full paper; o, open; pc, placebo controlled; PICP, procollagen type 1 carboxy-terminal propeptide; PIIINP, amino terminal of type III collagen; PTH, parathyroid hormone; r, randomized.

a Number of patients who completed the trial.
b Duration of treatment with each active treatment.
c Administered with a spacer.
not specific to bone. Increased blood and/or urinary levels of calcium, phosphate and hydroxyproline indicate bone resorption, but there are concerns over the sensitivity and specificity of these markers (42). Studies relying on these measurements (11,16,24) may not have the sensitivity to detect small changes from baseline or differences between treatments.

Short-term steroid-induced bone loss may be compensated over time by mechanisms that restore the equilibrium between bone formation and resorption but which cannot replace the deficit in bone mass. This might explain the reduction in bone density but normal levels of markers of bone turnover observed in some studies (27). Conversely, several other studies (21,25,37) found that, although markers of bone turnover were altered after long-term use of high-dose inhaled steroids, bone density was not significantly reduced. Thus, abnormal serum or urinary marker levels do not necessarily mean later bone weakness or increased risk of fracture. Genetic factors, bone density before beginning treatment, activity levels, diet and hormonal status are also important determinants of bone loss. It may, therefore, be that certain groups of patients are more susceptible to clinically important bone loss during steroid treatment than others.

A final important consideration is inhaler design. Systemic absorption of inhaled corticosteroids can be a problem with pressurized MDIs, because the high velocity of particle delivery means that about 80% of the dose is deposited on the oropharyngeal mucosa (43) where it is available for uptake into the systemic circulation. Deposition is reduced to about 10–15% if a large-volume spacer is attached to the inhaler (44). Use of a spacer has been shown to lower the incidence of local steroid side-effects (45–47), and it is logical to assume that decreased availability for systemic absorption resulting from lower oropharyngeal deposition would reduce any effects on bone. Using the Turbuhaler® breath-actuated dry powder delivery system for budesonide results in reduced drug deposition in the mouth (by approximately 60%) compared with the MDI without a spacer (48). Thus, differences in systemic side-effects may reflect differences in inhaler technology. This might explain the apparent differences in effects on osteocalcin observed by Brown et al. (17) when using a MDI with and without a spacer. However, inclusion of a spacer does not always prevent systemic effects, as noted in several studies (7,16).

A dry powder inhaler for BDP, the Diskhaler®, has been available for some time and delivers comparable doses to the budesonide Turbuhaler® (49). Comparisons of the effects of inhaled corticosteroids on bone using these equivalent devices would help to provide a clearer picture of any differences between BDP and budesonide. To date, only one short-term study of this type in children (35) has been performed. Finally, rinsing the mouth with water after inhalation can remove 80% of the oropharyngeal deposit (45). Careful attention to inhalation technique can thus help to minimize any adverse systemic effects.

Conclusions

Studies in healthy adult volunteers and asthma patients of various ages have shown that both BDP and budesonide can cause changes in markers of bone turnover, especially osteocalcin, when inhaled at high doses. While these changes are suggestive of bone loss, bone density studies in asthma patients after long-term treatment have produced conflicting results. Inhaled steroids have considerably fewer adverse effects on bone than oral steroids, but the threshold dose at which they begin to affect bone remains unclear. Direct comparisons suggest that budesonide may exert less effect on bone turnover than BDP, but studies with adequate controls for previous corticosteroid use, asthma severity, activity levels and type of inhaler are required to confirm these differences. Prospective, long-term measurements of bone density are also required to establish whether changes in markers of bone turnover translate into an increased risk of osteoporosis and fractures, particularly in patients with increased susceptibility resulting from genetic factors, age or hormonal status.

References


