

Review

## Effects of inhaled corticosteroids on bone

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### Abstract

Inhaled corticosteroids (ICS) are the most effective therapy for asthma currently available. The increasing use of ICS raises the issue of possible adverse systemic effects. Since one of the most important side-effects of oral corticosteroids (OCS) is osteoporosis, this article focuses on current knowledge of the effects of ICS on bone. Generally, doses higher than 1.0 mg/day cause a dose-dependent decrease in serum osteocalcin levels. Decreases in bone density have been suggested after treatment with ICS, but in most studies it is impossible to quantify the contribution of previous treatment with OCS and other confounding factors to bone loss. The clinical relevance of the observed changes in the long term is unknown. To date, no fracture data have been reported in patients. Beclomethasone dipropionate, budesonide and fluticasone propionate do not appear to be different per milligram ICS. In general, the lowest clinically efficacious dosage of ICS should be aimed at.

*Keywords:* Asthma; Inhaled corticosteroids; Side-effects; Osteoporosis; Bone metabolism

### 1. Introduction

Bronchial asthma is a frequently occurring disease, affecting about 5% of the adult population and 10–15% of children [1]. Inhaled corticosteroids (ICS) are the most effective therapy for asthma currently available [2,3]. These agents suppress the chronic inflammatory process, which is a pathological hallmark of this disease in the airways [3,4].

ICS are effective in various types of asthma and at all ages [2–4]. The international consensus recommends ICS to be used in an early stage of asthma [5–7], as airway inflammation is also present in patients with mild symptoms. In addition, there is a tendency to prescribe ICS for a prolonged period of

time, as even after 2 years of treatment no plateau has been reached in effects [6–8]. Finally, there may be a dose-related improvement, since increasing the dose of ICS results in a greater improvement in the patients [9]. High-dose ICS may be used to control severe asthma and to reduce the need for oral corticosteroids (OCS) [10,11]. In Europe, the ICS mostly used are beclomethasone dipropionate (BDP), budesonide (BUD), and fluticasone propionate (FP).

In line with the above-mentioned arguments, the international guidelines recommend ICS in an early stage of asthma, and there is a clear tendency to prescribe ICS for a prolonged period of time and at high doses. This change in prescription raises the issue of safety and potential adverse systemic effects. Indeed, high dosages are associated with systemic effects, such as adrenocortical suppression [4], and, in children, decrease of growth [12]. The other poten-

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tially serious side-effect of ICS concerns bone metabolism and bone quality in the long term [13]. Osteoporosis is one of the most important side-effects of long-term treatment with OCS [14]. In this review we will focus on the currently known effects of ICS on bone.

## 2. Side-effects: general considerations

Only 10–15% of an inhaled dose of ICS reaches the target cells in the lower airways. The remaining part stays in the inhaler or is deposited in the oropharyngeal cavity. This may cause *local* side-effects, such as dysphonia and oral candidiasis [15]. The incidence of thrush varies from 5 to 20%, and is related to the dose of ICS. Dysphonia is a much more common problem and may be due to local myopathy of laryngeal muscles [16].

The amount of ICS that reaches the systemic circulation, and therefore causes the *systemic* side-effects, is derived mainly (> 80%) from the part of ICS that is absorbed from the lung. The remainder comes from the fraction deposited in the oropharynx, which is swallowed and subsequently absorbed via the gastrointestinal tract [17]. The amount of ICS that reaches the systemic circulation in this way is small as a result of rapid biotransformation in the liver [18], and can be further reduced by the use of a large volume spacer or by mouth rinsing.

## 3. Effects of steroids on bone

### 3.1. Biochemical markers of bone turnover

One of the most important side-effects of corticosteroids is osteoporosis. Osteoporosis may affect up to 50% of patients on maintenance treatment with OCS [19]. OCS inhibit the intestinal absorption of calcium (Ca) and phosphate and may increase urinary Ca excretion. The resulting decrease in serum Ca evokes secondary hyperparathyroidism, which is reflected in an increased serum level of PTH [20]. OCS also decrease bone formation, as reflected by a decrease in alkaline phosphatase, osteocalcin and procollagen type 1 carboxy-terminal propeptide (P1CP) [20–23]. In addition, OCS possibly also increase bone resorp-

tion, reflected in an increase in urinary Ca/creatinine and hydroxyproline/creatinine ratios [20,23] (Fig. 1). These changes lead to secondary osteoporosis and a rise in (non-traumatic) fracture incidence [19,20,24].

ICS interact with the same glucocorticoid receptors, and would therefore be expected to act along a similar pathway after systemic absorption. No significant effects on calcium or phosphate metabolism, however, were observed in adults in doses up to 2.4–3.2 mg/day for short periods of time [14,25]. Similarly, no changes were found in children treated with doses up to 0.8 mg/day [26,27].

Indices of bone formation, such as alkaline phosphatase (AP) or the bone-specific isoenzyme of AP, were not altered by ICS in most studies [25–31]. Only in the study of Ali et al. were changes found [32]. In this study in 8 healthy volunteers, a small decrease in AP was found after treatment with BDP 2.0 mg/day for 4 weeks, whereas after BUD 1.8 mg/day ( $n = 8$ ) no changes were observed. The significance of this open and small study is furthermore limited because of inaccurate statistical analysis. Kerstjens et al. [33] found no differences in AP after 4 weeks treatment with at least 0.8 mg of BDP or BUD.

In contrast, studies with a wash-out or placebo period, or with a control group without ICS, showed a dose-dependent decrease of the serum osteocalcin level, currently the most commonly used marker of bone formation [34] (Fig. 2) [21,25–31,35–38]. Osteocalcin is a very sensitive marker of osteoblast activity, as most serum osteocalcin originates from new cellular synthesis [34]. Osteocalcin is a specific marker of bone formation in processes with uncou-

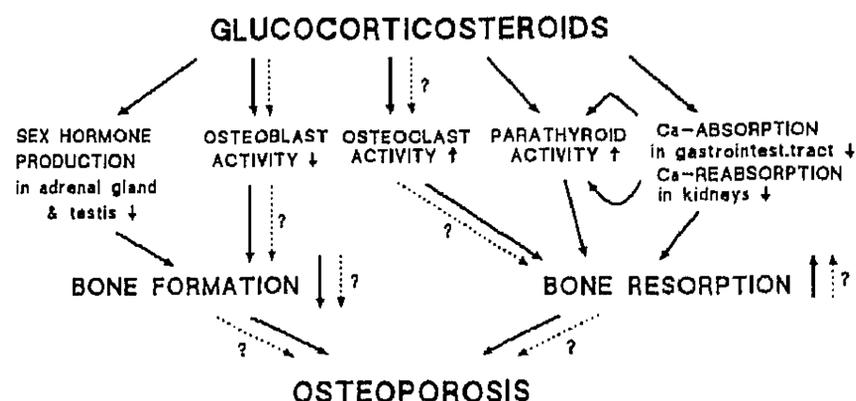


Fig. 1. Overview of the effects of oral corticosteroid (OCS) and inhaled corticosteroids (ICS) on bone metabolism and bone structure. Solid arrows = OCS; dotted lines = ICS.

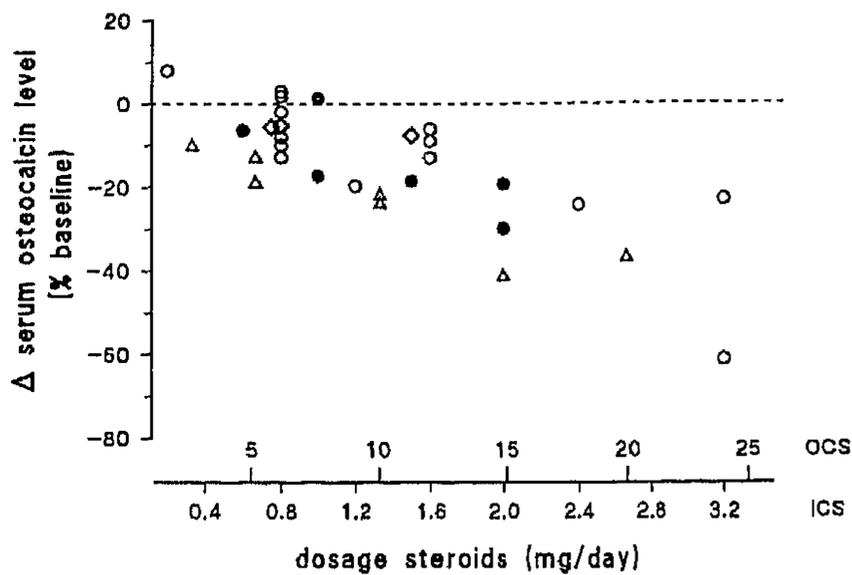


Fig. 2. Changes in serum osteocalcin level as a result of inhaled corticosteroids (ICS) and equipotent doses of oral corticosteroids (OCS). ○ = budesonide; ● = beclomethasone dipropionate; ◇ = fluticasone propionate; △ = oral prednisone. The symbols represent the outcomes in different studies [21,25–31,35–38].

pled bone formation and resorption, as is the case in glucocorticoid-induced osteoporosis [34,39].

No differences between BDP, BUD and FP appear to exist. From the same studies, effects of 'systemic equivalent doses' of OCS [40] are included in Fig. 2, showing the advantage of ICS. However, when looking at comparative trials between FP in half the dose of BDP, being clinically equipotent [41,42], osteocalcin levels were significantly lowered after the double dose of BDP, with no change after FP [31,43]. Ayres et al. [44] compared FP with BUD, but all patients already used 1–2 mg of ICS daily before the study. FP 1.0 and 2.0 mg, and BUD 1.6 mg daily did not change osteocalcin levels significantly. New markers of bone formation such as collagen type I extension peptides (P1CP) have shown no clear advantage over osteocalcin [34].

Markers of bone resorption, such as excretion of calcium and hydroxyprolines in urine, appeared to be increased in one study [32], but were unaltered in most studies [21,25,26,30,31,33,37]. Other markers of bone resorption include type 1 carboxy-terminal telopeptide (1CTP) and (deoxy)pyridinoline cross-links [34,39]. 1CTP measures the degradation of mature type I collagen (containing pyridinoline cross-links). 1CTP has been found to increase in diseases that degrade the surface (cortical part) of bone tissue (e.g., rheumatoid arthritis, bone metastasis), and changes only a little when trabecular bone is affected as in the case of glucocorticoid therapy

[39]. Changes in trabecular bone are better reflected in the concentration of cross-links, and deoxypyridinoline is more specific for osseous tissue than are pyridinoline cross-links [34]. To date, only a few data are available on the effects of ICS on pyridinoline excretion in asthmatic patients, showing no changes [31,45]. Altogether, these findings indicate that in general ICS do not increase bone resorption.

The long-term effects of ICS on bone metabolism are unclear. Kerstjens and colleagues [33] reported that long-term treatment with ICS did not affect biochemical markers of bone metabolism. P1CP and 1CTP remained unchanged after 2.5 years of treatment with 0.8 mg BDP daily. Long-term studies with higher dosages of ICS have not been reported to our knowledge.

### 3.2. Bone mineral density

Low bone mass is an essential feature of osteoporosis. The clinical diagnosis of osteoporosis requires the presence of at least one atraumatic fracture [46]. Measuring bone mineral density – by different techniques at different sites – is of prognostic relevance. In general, a reduction in bone mineral density by one standard deviation increases the risk of a fracture by 50–100% [47].

OCS in doses of 7.5 mg/day or more cause significant loss of bone in most patients, with a significantly greater loss of trabecular than of cortical bone. There is a relationship between rate of bone loss and OCS dose, with bone loss of up to 8% per year in doses of 8–17 mg/day and up to 17.5% in doses up to 25 mg/day [48]. However, lower doses of OCS may also have increased rates of bone loss [48,49]. Data suggest that bone loss is most pronounced in the early weeks of OCS therapy with subsequent slowing during prolonged treatment [48]. Up to 50% of patients on maintenance treatment with OCS may experience (non-traumatic) fractures in the long term [19,20,24,48].

Reductions in bone mineral density have also been suggested after treatment with ICS. Only a few studies have been conducted in patients who had previously (virtually) not been treated with OCS. A group of 26 children who had used ~ 0.6 mg (range 0.4–0.8) BDP daily for a period of 2 years showed

no changes compared to a control group [27]. On the other hand, a cross-sectional study in a group of 18 adult asthmatics, treated with at least 0.8 mg BDP or BUD for 1 year, showed a significant reduction in Z-score of the femoral head, compared with 18 asthmatics never having used ICS [13]. Serum osteocalcin was also significantly lower in the ICS-treated group than in the asthma control group. Again, there were no changes in AP or in urinary pyridinoline and deoxypyridinoline. Dose and duration of treatment with ICS correlated negatively with bone mineral density.

Most studies examining changes in bone mineral density in patients with asthma are flawed because of failure to control for previous OCS use [46,50,51]. In other studies, the dose of ICS was probably too low to cause changes [52,53]. The previous use of OCS, however, may be the most important factor influencing bone mineral density, besides other factors such as increased age, inactivity, smoking, malnutrition, menopausal status and genetic predisposition. Finally, asthma itself may lower bone mineral density [45].

Recently, Pauwels et al. [43] demonstrated that changing existing therapy with ICS (either BDP or BUD) to half the dose with FP resulted in a significant recovery of trabecular bone mineral density in Ward's triangle. This would be a confirmation that ICS really affect bone. Extensive data in this respect, however, have to be awaited.

### 3.3. Comparison between BDP, BUD and FP

The risk/benefit ratio of inhaled steroids is determined by the ratio of local (airway) efficacy versus systemic glucocorticoid activity. There are clear differences between the existing ICS with respect to *pharmacokinetic properties*. In the lung, BDP is hydrolysed to its much more active metabolite, beclomethasone-17-monopropionate (17-BMP) [54]. Metabolism of BUD and FP does not occur in the lung [38,55]. Systemic effects may also arise from absorption of the drugs from the oropharynx and from the gut after swallowing. ICS have an extensive first-pass metabolism in the liver, converting the ICS into hardly active or non-active metabolites. BUD is transformed 2–4 times more rapidly than 17-BMP, with an oral systemic bioavailability of 11% [55].

The hepatic excretion ratio of FP is almost 100%, resulting in an oral bioavailability of < 1% [56].

In models of inflammation, BUD showed a 2–4 times higher *local anti-inflammatory activity* than BDP [57,58]. FP showed twice the activity of BDP and BUD in one study, another found no significant differences between FP and BUD [59,60]. However, the extent to which these differences are also of clinical importance must be deduced from studies comparing these drugs on relevant parameters. With regard to *clinical efficacy* of BDP and BUD, no differences were shown over a wide dosage interval (0.4–1.5 mg), when compared in similar dosages and forms of administration, both in adults [11,61–66] and in children [67–69]. Even with different dosages and a difference in deposition in the airways, these studies also did not show any difference in clinical efficacy between the two preparations. The majority of comparable trials of FP (although mostly assessed against BDP) confirm preclinical data suggesting a higher clinical potency of FP over a wide dosage range (for review, see [41,70]).

With regard to the systemic effects, the negligible oral bioavailability of FP compares favourably with the other ICS. However, as the majority of the systemic available dose reaches the bloodstream after absorption from the lungs, assessment of overall systemic activity remains necessary. There appear to be no differences in systemic effects of the 3 ICS in equal dosages (Fig. 2). However, there appears to be a clear dose-related increase in systemic effects. As FP on a milligram base is more potent than BDP (and possibly BUD [70], this offers the ability to deliver lower dosages with similar clinical efficacy, leading to less effect on bone structure and metabolism.

## 4. Conclusion

The short- and long-term clinical efficacy of ICS in asthmatics has now been proved convincingly. With regard to higher dosages, it cannot be excluded that these drugs have adverse effects on bone in the long term. Dose-dependent changes in parameters of bone metabolism indicate systemic effects in the short term, but the course after long-term treatment is unknown. Furthermore, the relationship of these

changes to bone quality is speculative. It still needs to be determined whether changes in bone turnover actually signify an increased fracture risk in the long term. To date, this has not been observed in clinical practice. Clearly, more controlled studies are needed since no definitive answer has been given. Measuring indices of bone metabolism and bone mineral density in patients treated with only ICS should not be used so far in clinical practice. Nevertheless, an increasing number of studies report effects of ICS on bone. In this respect, the lack of short-term effects on bone metabolism by FP, in contrast to clinically equipotent dosages of BDP, may be of potential interest.

In the meantime, caution is desirable when administering high dosages of ICS over a long period of time, since there are differences in individual sensitivity to ICS. The lowest possible dosage of ICS that has a clinically optimal effect on symptoms, lung function and bronchial hyperresponsiveness should be aimed at.

## References

- [1] Alabaster VA, Moore BA. Drug intervention in asthma: present and future. *Thorax* 1993;48:176–182.
- [2] Barnes PJ. A new approach to the treatment of asthma. *N Engl J Med* 1989;321:1517–1527.
- [3] Barnes PJ. Anti-inflammatory therapy for asthma. *Annu Rev Med* 1993;44:229–242.
- [4] Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma. *Am Rev Respir Dis* 1993;148:S1–S26.
- [5] Guidelines on the management of asthma. *Thorax* 1993;48:S1–S24.
- [6] Juniper EF, Kline PA, Vanzieleghem MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in non-steroid dependent asthmatics. *Am Rev Respir Dis* 1990;142:832–836.
- [7] Haahtela T, Jarvinen M, Kava T. Comparison of a  $\beta_2$ -agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med* 1991;325:388–392.
- [8] Kerstjens HAM, Brand PLP, Hughes MD, et al. A comparison of bronchodilator therapy with or without inhaled corticosteroid therapy for obstructive airways disease. *N Engl J Med* 1992;327:1413–1419.
- [9] Juniper EF, Kline PA, Van Zieleshem MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Long-term effects of budesonide on airway responsiveness and clinical asthma severity in inhaled steroid-dependent asthmatics. *Eur Respir J* 1990;3:1122–1227.
- [10] Smith MJ, Hodson ME. High-dose beclomethasone inhaler in the treatment of asthma. *Lancet* 1983;i:265–269.
- [11] Rafferty P, Tucker LG, Frame MH, Fergusson RJ, Biggs B-A, Crompton GK. Comparison of budesonide and beclomethasone dipropionate in patients with severe chronic asthma: assessment of relative prednisolone-sparing effects. *Br J Dis Chest* 1985;79:244–250.
- [12] Zeitlin SR, Crowley S, Hindmarsh PC, Brook CGD. Inhaled corticosteroids and growth. *Eur Respir Rev* 1993;3(13):333–337.
- [13] Hanania NA, Chapman KR, Sturtridge WC, Szalai JP, Kesten S. Dose related decrease in bone density among asthmatic patients treated with inhaled corticosteroids. *J Allergy Clin Immunol* 1995;96:571–579.
- [14] Toogood JH, Crilly RG, Jones G, Nadeau J, Wells GA. Effect of high-dose inhaled budesonide on calcium and phosphate metabolism and the risk of osteoporosis. *Am Rev Respir Dis* 1988;138:57–61.
- [15] Toogood JH, Jennings B, Greenway RW, Chuang L. Candidiasis and dysphonia complicating beclomethasone treatment of asthma. *J Allergy Clin Immunol* 1980;65:145–153.
- [16] Williams AJ, Baghat MS, Stableforth DE, Cayton RM, Shenoi PM, Skinner C. Dysphonia caused by inhaled steroids: recognition of a characteristic laryngeal abnormality. *Thorax* 1983;38:813–821.
- [17] Pedersen S, Steffensen G, Ohlsson SV. The influence of orally deposited budesonide on the systemic availability of budesonide after inhalation from a Turbuhaler®. *Br J Clin Pharmacol* 1993;36:211–214.
- [18] Stiksa G, Glennow C, Johannesson N. An open cross-over trial with budesonide and beclomethasone dipropionate in patients with bronchial asthma. *Eur J Respir Dis* 1982;63:266–267.
- [19] Adinoff AD, Hollister JR. Steroid-induced fractures and bone loss in patients with asthma. *N Engl J Med* 1983;309:265–267.
- [20] Reid IR. Pathogenesis and treatment of steroid osteoporosis. *Clin Endocrinol* 1989;30:83–103.
- [21] Jennings BH, Andersson KE, Johansson SÅ. Assessment of systemic effects of inhaled budesonide and oral prednisolone on adrenal function and markers of bone turnover. *Eur J Clin Pharmacol* 1991;40:77–82.
- [22] Oikarinen A, Autio P, Vuori J, et al. Systemic glucocorticoid treatment decreases serum concentrations of carboxyterminal propeptide of type I procollagen and aminoterminal propeptide of type III procollagen. *Br J Dermatol* 1992;126:172–178.
- [23] Morrisson D, Ali NJ, Routledge PA, Capewell S. Bone turnover during short course prednisolone treatment in patients with chronic obstructive airways disease. *Thorax* 1992;47:418–420.
- [24] Worth H, Stammen D, Keck E. Therapy of steroid-induced bone loss in adult asthmatics with calcium, vitamin D, and diphosphonate. *Am J Respir Crit Care Med* 1994;150:394–397.
- [25] Hodsman AB, Toogood JH, Jennings B, Fraher LJ, Baskerville JC. Differential effects of inhaled budesonide and

- oral prednisolone on serum osteocalcin. *J Clin Endocrinol Metab* 1991;72:530–540.
- [26] Wolthers OD, Riis BJ, Pedersen S. Bone turnover in asthmatic children treated with oral prednisolone or inhaled budesonide. *Pediatr Pulmonol* 1993;16:341–346.
- [27] König P, Hillman L, Cervantes C, et al. Bone metabolism in children with asthma treated with inhaled beclomethasone dipropionate. *J Pediatr* 1993;122:219–226.
- [28] Meeran K, Hattersley A, Burrin J, Shiner R, Ibbertson K. Oral and inhaled corticosteroids reduce bone formation as shown by plasma osteocalcin levels. *Am Rev Respir Dis* 1995;151:333–336.
- [29] Sorva R, Turpeinen M, Juntunen-Backman K, Karonen S-L, Sorva A. Effects of inhaled budesonide on serum markers of bone metabolism in children with asthma. *J Allergy Clin Immunol* 1992;90:808–815.
- [30] Puolijoki H, Liippo K, Herrala J, Salmi M, Risteli J, Tala E. Does high dose inhaled beclomethasone effect the calcium metabolism?. *Eur Respir J* 1991;4:483s.
- [31] Bootsma GP, Dekhuijzen PNR, Festen J, Mulder PGH, Swinkels LMJW, Van Herwaarden CLA. Fluticasone propionate does not influence bone metabolism in contrast to beclomethasone dipropionate. *Am J Respir Crit Care Med* 1996;153:924–930.
- [32] Ali NJ, Capewell S, Ward MJ. Bone turnover during high dose inhaled corticosteroid treatment. *Thorax* 1991;46:160–164.
- [33] Kerstjens HAM, Postma DS, Van Doormaal JJ, et al. Effects of short-term and long-term treatment with inhaled corticosteroids on bone metabolism in patients with airways obstruction. *Thorax* 1994;49:652–656.
- [34] Van Daele PLA, Birkenhäger JC, Pols HAP. Biochemical markers of bone turnover: an update. *Neth J Med* 1994;44:65–72.
- [35] Leech JA, Hodder RV, Ooi DS, Gay J. Effects of short-term inhaled budesonide and beclomethasone dipropionate on serum osteocalcin in premenopausal women. *Am Rev Respir Dis* 1993;148:113–135.
- [36] Pouw EM, Prummel MF, Oosting H, Roos CM, Endert E. Beclomethasone inhalation decreases serum osteocalcin concentrations. *Br Med J* 1991;302:627–628.
- [37] Toogood JH, Jennings B, Hodsmann AB, Baskerville J, Fraher LJ. Effects of dose and dosing schedule of inhaled budesonide on bone turnover. *J Allergy Clin Immunol* 1991;88:572–580.
- [38] Grove A, Allam C, McFarlane LC, McPhate G, Jackson CM, Lipworth BJ. A comparison of the systemic bioactivity of inhaled budesonide and fluticasone propionate in normal subjects. *Br J Clin Pharmacol* 1994;38:527–532.
- [39] Ristelli L, Ristelli J. Biochemical markers of bone metabolism. *Ann Med* 1993;25:385–393.
- [40] Toogood JH, Baskerville J, Jennings B, Lefcoe NM, Johanson S-A. Bioequivalent doses of budesonide and prednisone in moderate and severe asthma. *J Allergy Clin Immunol* 1989;84:688–700.
- [41] Holliday SM, Faulds D, Sorkin EM. Inhaled fluticasone propionate: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in asthma. *Drugs* 1994;47:318–331.
- [42] Bootsma GP, Dekhuijzen PNR, Festen J, Mulder PGH, Van Herwaarden CLA. Comparison of fluticasone propionate and beclomethasone dipropionate on direct and indirect measurements of bronchial hyperresponsiveness in patients with stable asthma. *Thorax* 1995;49:1044–1050.
- [43] Pauwels RA, Demedts MG, Yernault JC, Geusens P, Roosen WA. Belgian multicentre study: Comparison of long-term safety and efficacy of fluticasone propionate and beclomethasone dipropionate in combination with salmeterol in patients with moderate to severe asthma. *Am J Respir Crit Care Med* 1995;151:A276.
- [44] Ayres JC, Bateman ED, Lundback B, Harris TAJ. International Study Group: High dose fluticasone propionate, 1 mg daily, versus fluticasone propionate, 2 mg daily, or budesonide, 1.6 mg daily, in patients with chronic severe asthma. *Eur Respir J* 1995;8:579–586.
- [45] Packe GE, Douglas JG, McDonald AF, Robins SP, Reid DM. Bone density in asthmatic patients taking high dose inhaled beclomethasone and intermittent systemic corticosteroids. *Thorax* 1992;47:414–417.
- [46] Conference report. Consensus development conference: Prophylaxis and treatment of osteoporosis. *Am J Med* 1991;90:107–110.
- [47] Desforges JF. Clinical use of bone densitometry. *N Engl J Med* 1991;324:1105–1109.
- [48] Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis: pathogenesis and management. *Ann Intern Med* 1990;112:352–364.
- [49] Saito JK, Davis JW, Wasnich RD, Ross PD. Users of low-dose glucocorticoids have increased bone loss rates: a longitudinal study. *Calcif Tissue Int* 1995;57:115–119.
- [50] Ip M, Lam K, Yam L, Kung A, Ng M. Decreased bone mineral density in premenopausal asthma patients receiving long-term inhaled steroids. *Chest* 1994;105:1722–1727.
- [51] Reid DM, Nicoll JJ, Smith MA, Higgins B, Tohill P, Nuki G. Corticosteroids and bone mass in asthma; comparisons with rheumatoid arthritis and polymyalgia rheumatica. *Br Med J* 1986;293:1463–1466.
- [52] Luengo M, Del Rio L, Guanabens N, Picado C. Long-term effect of oral and inhaled glucocorticoids on bone mass in chronic asthma. A two year follow-up study. *Eur Respir J* 1991;4:342s.
- [53] Wolff AH, Adelsberg B, Aloia J, Zitt M. Effect of inhaled corticosteroid on bone density in asthmatic patients: a pilot study. *Ann Allergy* 1991;67:117–121.
- [54] Wurthwein G, Rhodewald P. Activation of beclomethasone dipropionate by hydrolysis to beclomethasone-17-monopropionate. *Biopharmacol Drug Dispos* 1990;11:381–394.
- [55] Ryrfeldt Å, Andersson P, Edsbäcker S, Tönnesson M, Davies D, Pauwels R. Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid. *Eur J Respir Dis* 1982;63(suppl):86–95.
- [56] Harding SM. The human pharmacology of fluticasone propionate. *Respir Med* 1990;84:25–29.
- [57] Johansson SÅ, Andersson K-E, Brattsand R, Gruvstad E,

- Hedner P. Topical and systemic glucocorticoid potencies of budesonide and beclomethasone dipropionate in man. *Eur Acad Allergol Clin Immunol* 1982;2:709–715.
- [58] Brattsand R, Thalén A, Roempke K, Källstrom L, Gruvstad E. Development of new glucocorticosteroids with a very high ratio between topical and systemic activities. *Eur J Respir Dis* 1982;63(suppl 122):62–73.
- [59] English AF, Neate MS, Quint DJ, Sareen M. Biological activities of some corticosteroids used in asthma. *Am J Respir Crit Care Med* 1994;149:A212.
- [60] Anderson N, Klint S, Randwall G, Wiren JE. Equipotency of budesonide and FP (Abstract). *Am J Respir Crit Care Med* 1994;149:A467.
- [61] Björkander J, Formgren H, Johansson SÅ, Millqvist E. Methodological aspects on clinical trials with inhaled corticosteroids: results of two comparisons between two steroid aerosols in patients with asthma. *Eur J Respir Dis* 1982;63(suppl 122):108–117.
- [62] Boe J, Rosenhall L, Alton M, Carlsson L-G, Carlsson U, Hermansson B-A. Comparison of dose–response effects of inhaled beclomethasone dipropionate and budesonide in the management of asthma. *Allergy* 1989;44:349–355.
- [63] Petrie GR, Choo-Kang YFJ, Clark RA, Milledge JS, Studdy PR, Whitfield RJ. An assessment of the acceptability of two breath-actuated corticosteroid inhalers. Comparison of Turbohaler with Diskhaler. *Drug Invest* 1990;2:129–131.
- [64] Willey RF, Godden DJ, Carmichael J, Preston P, Frame M, Crompton GK. Comparison of twice daily administration of a new corticosteroid budesonide with beclomethasone dipropionate four times daily in the treatment of chronic asthma. *Br J Dis Chest* 1982;76:61–68.
- [65] Ebden P, Jenkins A, Houston G, Davies BH. Comparison of two high dose corticosteroid aerosol treatments, beclomethasone dipropionate (1500 µg/day) and budesonide (1600 µg/day), for chronic asthma. *Thorax* 1986;41:869–874.
- [66] Svendsen UG, Frolund L, Heinig JH, Madsen F, Nielsen NH, Weeke B. High-dose inhaled steroids in the management of asthma. *Allergy* 1992;47:174–180.
- [67] Springer C, Avital A, Maayan CH, Rosler A, Godfrey S. Comparison of budesonide and beclomethasone dipropionate for treatment of asthma. *Arch Dis Child* 1987;62:815–819.
- [68] Baran D. A comparison of inhaled budesonide and beclomethasone dipropionate in childhood asthma. *Br J Dis Chest* 1987;81:170–175.
- [69] Field HV, Jenkinson PMA, Frame MH, Warner JO. Asthma treatment with a new corticosteroid aerosol, budesonide, administered twice daily by spacer inhaler. *Arch Dis Child* 1982;57:864–866.
- [70] Barnes N, Hallett C, Harris TAJ. An overview of morning peak expiratory flow rate (PEFR) for clinical trials comparing fluticasone propionate (FP) with budesonide (BUD). *Eur Respir J* 1996;9(suppl 23):52s.