Inhaled Steroids for the Treatment of Asthma and Risk of Osteoporosis

Kemp JP, Osur S, Shrewsbury SB, et al. Potential effects of fluticasone propionate on bone mineral density in patients with asthma: a 2-year randomized, double-blind, placebo-controlled trial. Mayo Clin Proc 2004;79:458–66.

Study Overview

Objective. To determine the effects of fluticasone propionate on bone mineral density (BMD), hypothalamic-pituitary-adrenal (HPA) axis function, and ocular change.

Design. Randomized, double-blind, placebo-controlled trial with an intention-to-treat analysis.

Setting and participants. Participants were recruited from asthma and allergy clinics and evaluated from July 1994 through June 1997. Eligible patients were men aged 18 to 50 years and women aged 18 to 40 years who met the following criteria: ≥ 6 months of stable and relatively mild asthma (mean forced expiratory volume in 1 second, 82%–85% of predicted) with a low likelihood of requiring oral corticosteroids; normal stimulated cortisol response; normal BMD; no evidence of glaucoma, cataracts, or blindness; no use of corticosteroids for 1 month prior to screening; and a lifetime use of corticosteroids of ≤ 4 weeks. Patients with Cushing's or Addison's disease, any disorder of calcium metabolism, rheumatoid arthritis, osteoarthritis, any metabolic bone disease, anorexia, morbid obesity, unexplained weight loss, or substance abuse were excluded. Patients on hormone replacement therapy or glucocorticoid therapy, or taking vitamin D supplements, digitalis, ketoconazole, or calcitonin also were excluded.

Intervention. Participants were randomized to 88 µg or 440 µg of fluticasone propionate administered via metered-dose inhaler twice daily without a spacer, or placebo.

Main outcome measures. The primary outcomes were BMD, HPA axis functioning, and ocular toxicity. BMD was determined through dual energy x-ray absorptiometry (DEXA) and serum osteocalcin. DEXA scans of the lumbar spine were performed for primary analysis, and proximal femur and total body DEXA scans were performed as a secondary measure. To assess the function of the HPA axis, cortisol production was assessed during a 6-hour cotropin infusion test. Ocular toxicity was evaluated by applanation tonometry, slit-lamp lens examinations, and direct funduscopy. Outcomes were assessed at baseline (during a 21-day, single-blind, placebo run-in period) and then every 24 weeks over the entire course of the study (104 weeks).

Main results. 190 patients were screened and 160 were randomized. Baseline demographic characteristics were similar between the 3 groups. 54 patients were allocated to the placebo group and 40 (74%) completed the trial. 55 patients were assigned to receive fluticasone propionate at 88 µg and 32 (58%) completed the trial, while 51 individuals received fluticasone at 440 µg and 26 (51%) completed the trial. Mean BMD did not differ between the 3 groups at baseline or after 2 years of treatment. Patients randomized to fluticasone 440 µg had a statistically significant difference in peak cosyntropin-stimulated plasma cortisol at weeks 24 and 52. These differences only represented a 10% to 13% reduction from baseline. This difference was not seen at weeks 76 or 104. No clinically important changes in findings in ophthalmic examination were seen over the duration on the study. 14% of subjects receiving fluticasone 440 µg developed oral candidiasis compared with 2% and 0% in the fluticasone 88 µg and placebo groups, respectively.

Conclusion. Treatment of asthma for 2 years with 88 µg of fluticasone twice daily resulted in similar effects on bone, eye, and HPA axis function when compared with placebo. Larger doses of fluticasone (440 µg twice daily) did transiently reduce serum cortisol levels but had no effect on BMD. Neither dose resulted in any ocular changes.

Commentary

Corticosteroids have an important role in the treatment of severe asthma. Toxicities associated with oral corticosteroids prompted the search for safer long-term alternatives. Inhaled corticosteroids, through topical delivery, are believed to offer the anti-inflammatory properties of oral corticosteroids without the systemic side effects. Inhaled corticosteroids have been so effective in the treatment of asthma that they have become the mainstay of treatment [1]. How-

ever, very few well-designed trials have been conducted to determine if inhaled steroids produce some of the similar systemic toxicities of oral corticosteroids over longer treatment periods. Kemp et al have conducted a trial to determine if long-term use of inhaled corticosteroids for asthma results in osteoporosis or adrenal insufficiency.

Important systemic toxicities associated with oral corticosteroids (ie, osteoporosis, cataracts, HPA axis disruption) often have resulted in significant morbidity for asthmatics with uncontrolled disease. This study adds to an emerging literature that has demonstrated the safety of inhaled corticosteroids for both short-term and long-term administration. It is important to note that different inhaled steroids have different oral bioavailabilities and selectivity for the glucocorticoid receptor, and these results cannot be extrapolated to other inhaled corticosteroids. However, other studies have demonstrated that inhaled corticosteroids have little effect on BMD [2,3]. Therefore, it seems probable that inhaled corticosteroids in general, particularly low-dose formulations, do not result in long-term adverse effects on bone metabolism. In addition, the inclusion and exclusion criteria used for sample selection for this study were very restrictive. This produced a homogenous population with little to no risk factors for osteoporosis. Whether inhaled corticosteroids contribute to the development of osteoporosis in individuals with greater susceptibility is unknown.

Applications for Clinical Practice

Fluticasone propionate appears to have no clinically important effects on BMD, HPA axis function, or eye function over a 2-year period. Although the reduction of serum cortisol levels at higher doses of fluticasone was not clinically significant and only transient, it supports the recommendation to taper asthmatics to the lowest inhaled corticosteroid dose necessary to achieve optimal symptom control.

–Review by Harvey J. Murff, MD, MPH

References

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3. Hughes JA Conry BG, Male SM, Eastell R. One year prospective open study of the effects of high dose inhaled steroids, fluticasone propionate, and budesonide on bone markers and bone mineral density. Thorax 1999;54:223–9.