High sodium intake is not an osteoporosis risk factor

The relationship between dietary salt intake and bone mineral density (BMD) was evaluated to test the hypothesis that high dietary sodium intake, resulting in sodium-mediated excretion of renal calcium, is a risk factor for osteoporosis.

The study subjects were 258 women (average age, 73.3 years) and 169 men (average age, 72.4 years). A 24-hour diet recall was done for the period 1973 through 1975; follow-up bone mineral density of the ultradistal radius, midradius, total hip, and spine was measured between 1988 and 1991. Covariates were ascertained by self-report and examination at baseline. Multivariable analysis of the sodium-BMD association was performed using gender and menopause-specific linear regressions.

In both male and female subjects, higher levels of sodium intake were strongly associated with higher levels of calcium intake and total calories. Body mass index increased with sodium quartile in women, whereas a modest negative association was seen in men. In women, after age adjustment, positive associations between dietary sodium and bone density were found at the ultradistal radius and the total hip. Bone mineral density increased by 0.01 g/cm^2 to 0.02 g/cm^2. After adjustment for estrogen use, body mass, dietary calcium, alcohol, and total calories, these effects were no longer significant. Similar patterns were seen in premenopausal and postmenopausal women. In men, age and multivariate-adjusted BMD increased with higher sodium intake at the ultradistal radius only.

After control for confounders, a small statistically significant protective effect of sodium was found at the ultradistal radius in men only. At other sites in women and men, no effect of sodium on BMD was apparent in the multivariable models.

Although these results show a small beneficial effect of sodium on bone, there are many overriding public health reasons not to increase sodium intake. The results also suggest that sodium intake, in the range measured, is not a major osteoporosis risk factor.

Greendale GA, Barrett-Connor E, Edelstein S, et al: Dietary sodium and bone mineral density: Results of a 16-year follow-up study. *J Am Geriatr Soc* 1994; 42:1050-1055.

Medicare HMO versus fee-for-service on stage of cancer at diagnosis

Cancer patients in health maintenance organizations (HMOs) were compared with those patients covered under fee-for-service on stage at diagnosis. Most previous studies have found few differences between HMOs and fee-for-service on access to or quality of care.

The study examined stage at diagnosis for aged Medicare enrollees in HMOs and fee-for-service. The investigators used information from the Surveillance, Epidemiology, and End Results program, linked with Medicare enrollment files. Twelve cancer sites were investigated, and demographics, area of residence, year of diagnosis (1985 to 1989), and education at the census tract level were controlled.

Cancers of the female breast, cervix, colon, and melanomas were diagnosed in HMO enrollees at earlier stages and stomach cancer at later stages. No differences for cancers of the prostate, rectum, buccal cavity and pharynx, bladder, uterus, kidney, and ovary were found. HMO effects were found strongest in areas with large, mature HMOs.

The findings show that HMO enrollees, compared with fee-for-service enrollees, were diagnosed at earlier stages for cancer sites for which effective screening services are available.

Cancer screening and preventive services are often provided by HMOs with Medicare contracts but are not covered under fee-for-service.

Riley GF, Potosky AL, Lubitz JD, et al: Stage of cancer at diagnosis for Medicare HMO and fee-for-service enrollees. *Am J Public Health* 1994;84:1578-1604.

Effect of simvastatin on coronary atheroma

The Multicenter Anti-Atheroma Study (MAAS) began a double-blind clinical trial in 1987 to study the effects on coronary atheroma of reduction of plasma lipids. The tests involved the use of simvastatin relative to placebo in patients with moderate hypercholesterolemia and known coronary artery disease.

(continued on page 914)

Beclovent®
(beclomethasone dipropionate, USP)
Inhalation Aerosol
For Oral Inhalation Only

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Beclovent® Inhalation Aerosol product labeling.

CONTRAINDICATIONS: Beclovent® Inhalation Aerosol is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS:

Particular care is needed in patients who are transferred from systemically active corticosteroids to Beclovent® Inhalation Aerosol because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosol beclomethasone dipropionate. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infections, particularly gastroenteritis. Although Beclovent Inhalation Aerosol may provide control of asthmatic symptoms during these episodes, it does NOT provide the systemic steroid that is necessary for coping with these emergencies.

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning resting cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal only if it falls at or near the normal mean level.

Persons who are on drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in nonimmune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Localized infections with *Candida albicans* or *Aspergillus niger* have occurred frequently in the mouth and pharynx and occasionally in the larynx. Positive cultures for oral *Candida* may be present in up to 75% of patients. Although the frequency of clinically apparent infection is considerably lower, these infections may require treatment with appropriate antifungal therapy or discontinuation of treatment with Beclovent Inhalation Aerosol.

Beclovent Inhalation Aerosol is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

Patients should be instructed to contact their physician immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment with Beclovent Inhalation Aerosol. During such episodes, patients may require therapy with systemic corticosteroids.

There is no evidence that control of asthma can be achieved by the administration of Beclovent Inhalation Aerosol in amounts greater than the recommended doses.

Transfer of patients from systemic steroid therapy to Beclovent Inhalation Aerosol may unmask allergic conditions previously suppressed by the systemic steroid therapy, e.g., rhinitis, conjunctivitis, and eczema.

PRECAUTIONS: During withdrawal from oral steroids, some patients may experience symptoms of systemically active steroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function (see DOSAGE AND ADMINISTRATION).

In responsive patients, beclomethasone dipropionate may permit control of asthmatic symptoms without suppression of HPA function, as discussed below (see CLINICAL STUDIES). Since beclomethasone dipropionate is absorbed into the circulation and can be systemically active, the beneficial effects of Beclovent® Inhalation Aerosol in minimizing or preventing HPA dysfunction may be expected only when recommended dosages are not exceeded.

Because of the possibility of systemic absorption of orally inhaled corticosteroids, including beclomethasone, patients should be monitored for symptoms of systemic effects such as mental disturbances, increased bruising, weight gain, cushingoid features, and cataracts. Therefore, if such changes occur, Beclovent Inhalation Aerosol should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroids.

In addition, children should be monitored for a reduction in growth velocity, although the relationship between growth velocity and final adult height is not known.

The long-term effects of beclomethasone dipropionate in human subjects are still unknown. In particular, the local effects of the agent on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. There is also no information about the possible long-term systemic effects of the agent.

The potential effects of Beclovent Inhalation Aerosol on acute, recurrent, or chronic pulmonary infections, including active or quiescent tuberculosis, are not known. Similarly, the potential effects of long-term administration of the drug on lung or other tissues are unknown.

Pulmonary infiltrates with eosinophilia may occur in patients on Beclovent Inhalation Aerosol therapy. Although it is possible that in some patients this state may become manifest because of systemic steroid withdrawal when inhalational steroids are administered, a causative role for beclomethasone dipropionate and/or its vehicle cannot be ruled out.

Information for Patients: Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Pregnancy: ***Teratogenic Effects:*** Glucocorticoids are known teratogens in rodent species and beclomethasone dipropionate is no exception.

Teratology studies were done in rats, mice, and rabbits treated with subcutaneous beclomethasone dipropionate. Beclomethasone dipropionate was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and partial agenesis of the thymus. Well-controlled trials relating to fetal risk in humans are not available. Glucocorticoids are secreted in human milk. It is not known whether beclomethasone dipropionate would be secreted in human milk, but it is safe to assume that it is likely. The use of beclomethasone dipropionate in pregnant women, nursing mothers, or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother, embryo, or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for hypoadrenalism.

ADVERSE REACTIONS: Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosol beclomethasone dipropionate (see WARNINGS).

Suppression of HPA function (reduction of early morning plasma cortisol levels) has been reported in adult patients who received 1,600-mcg daily doses of Beclovent® Inhalation Aerosol for 1 month. A few patients on Beclovent Inhalation Aerosol have complained of hoarseness or dry mouth.

Rare cases of immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm, have been reported after the use of beclomethasone oral or intranasal inhalers.

DOSAGE AND ADMINISTRATION: Patients experiencing symptoms of systemically active steroid withdrawal should be encouraged to continue with the inhaler but should be watched carefully for objective signs of adrenal insufficiency such as hypotension and weight loss. If evidence of adrenal insufficiency occurs, the systemic steroid dose should be boosted temporarily and thereafter further withdrawal should continue more slowly.

Allen & Hanburys
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References:

1. *Medi-Span®*, April 1994.
2. Kerigan AT, Pugsley SO, Cockcroft DW, Hargreave FE. Substitution of inhaled beclomethasone dipropionate for ingested prednisone in steroid-dependent asthmatics. *Can Med Assoc J.* April 1977;116:867-871.
3. British Thoracic and Tuberculosis Association. A controlled trial of inhaled corticosteroids in patients receiving prednisone tablets for asthma. *Br J Dis Chest.* 1976;70:95-103.
4. Data on file, Glaxo Inc.

medi-notes
(continued)

For 4 years, 381 patients with coronary heart disease were assigned to treatment with diet and either simvastatin (20 mg/d) or placebo. Quantitative angiography was done at baseline, and after 2 and 4 years.

Patients taking simvastatin had a 23% reduction in serum cholesterol, a 31% reduction in low-density lipoprotein cholesterol, and a 9% increase in high-density lipoprotein cholesterol compared with placebo over 4 years.

On a per-patient basis, angiographic progression occurred less often in the simvastatin-treated group (41 patients vs 54 patients); and regression was more fre-quent (33 patients vs 20 patients). Significantly more new lesions and new total occlusions developed in the group receiving placebo (48 patients vs 28 patients and 18 patients vs 8 patients, res-pectively).

There was no difference in clinical outcome. The numbers of patients who died or had myocardial infarction were 16 and 14 in the group receiving placebo and the group receiving simvastatin, respectively. More patients underwent coronary angioplasty or revascularization in the group taking placebo than in the group taking simvastatin (34 patients vs 23 patients, respectively).

The trial results showed that simvastatin (20 mg/d) over 4 years reduces hyperlipidemia and slows progression of diffuse and focal coronary atherosclerosis.

MAAS investigators: Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS). *Lancet* 1994;344:633-638. ◆