CLINICAL RESEARCH STUDY

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Antihistamine Therapy and Bone Mineral Density: Analysis in a Population-Based US Sample

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ABSTRACT

BACKGROUND: Histamine may play an important role in bone turnover. The data regarding histamine 1 receptor antagonist (H1RA), histamine 2 receptor antagonist (H2RA), and bone mineral density in humans are sparse. We examined bone mineral density in subjects using histamine receptor antagonists in a representative US population-based sample from the Third National Health and Nutrition Examination Survey (1988-1994).

METHODS: Adult subjects aged 60 years and more using H1RA or H2RA who underwent dual energy x-ray absorptiometry scanning in the Third National Health and Nutrition Examination Survey were identified. We compared the femoral neck bone mineral density among users of these agents with nonusers in adjusted linear regression models that included known demographic, anthropometric, and medical risk factors for osteoporosis.

RESULTS: The mean age of the study subjects was 72.6 years; 52% were women and 59% were white. Among subjects with femoral neck bone mineral density measured, 199 used H1RAs, 297 used H2RAs, and 4162 were nonusers of histamine receptor antagonists. Femoral neck bone mineral density adjusting for age and gender and other covariates was slightly higher in H1RA users (0.74 g/cm^2) versus nonusers (0.72 g/cm^2; $P = .037$). H2RA users showed slightly lower adjusted bone mineral density compared with nonusers (0.69 g/cm^2 vs 0.72 g/cm^2; $P = .003$), but bone densities were similar between H2RA users and nonusers when daily calcium intake exceeded 800 mg per day.

CONCLUSION: Femoral neck bone mineral density may be higher in H1RA users than nonusers among older adults. H2RA users with reduced calcium intake had lower bone mineral density than nonusers.
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KEYWORDS: Bone mineral density; Calcium intake; Histamine receptor antagonists; NHANES III

A novel role of histamine for bone health has been suggested in mastocytosis and animal studies.[1] Excess histamine accelerated bone resorption, and osteoporosis has been observed in patients with systemic mastocytosis, in which proliferating mast cells release histamine.[2] In contrast, mast cell-deficient mice showed ineffective osteoclastic recruitment and retarded bone remodeling.[3] Blocking histamine uptake by histamine 1 receptor antagonist (H1RA) and histamine 2 receptor antagonist (H2RA) reduced bone resorption and decreased osteoclast activity in ovariectomized rats.[4,5] A mouse model of histamine deficiency increased osteoclast differentiation factor (ODF) and receptor activator of nuclear factor-kappaB ligand (RANKL) secretion but failed to develop effective osteoclastogenesis, in which histamine may be needed to co-stimulate RANKL.[6] These data suggest that histamine may modulate bone resorption through the osteoclastic pathway. The mechanism of H1RA and H2RA on bone remodeling in humans remains

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unclear, but blocking histamine receptors might retard osteoclastogenesis in humans.

Previous human studies show skeletal effects differ between H1RA and H2RA. H1RA is frequently used for nasal congestion and rhinorrhea,[7] and appears to counteract bone loss in subjects with allergy: H1RA users had less nontraumatic fractures compared with those allergic subjects not taking H1RA.[8] H2RA is a common acid suppressive therapy for peptic ulcer disease and gastroesophageal reflux disease (GERD). In contrast with H1RA, there may be a small increased risk of hip fracture in those using H2RA.[9] It is unclear whether calcium malabsorption causes bone loss in users of H2RA, similar to what is observed among users of proton pump inhibitors, which are associated with vertebral and nonvertebral fracture incidence.[9,10] Histamine receptor antagonists are widely used among older people at risk for osteoporosis, but human data on their medications and bone density are sparse. We thus examined the bone mineral density among subjects aged 60 years and older using H1RA and H2RA, and the bone density was compared with nonusers of these antihistamine products in a representative US population-based sample from the Third National Health and Nutrition Examination Survey (NHANES III: 1988-1994).

CLINICAL SIGNIFICANCE

- The use of histamine-1 receptor antagonists, such as diphenhydramine and loratadine, may increase bone mineral density.
- However, histamine-2 receptor antagonists, such as cimetidine and ranitidine, may reduce bone mineral density when calcium and vitamin D intake are inadequate.

MATERIALS AND METHODS

Data Source and Histamine Receptor Antagonist Use

NHANES III was conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention between 1988 and 1994. The sample represents the civilian, noninstitutionalized population of the United States.[11] Histamine receptor antagonists are widely used among an older population who tend to be vulnerable to fractures. We identified subjects aged 60 years and older who underwent femoral neck bone mineral density measurement and compared users of H1RA or H2RA with nonusers. This study includes subjects aged 60 years and older because NHANES performs bone density scans on this population. Subjects without a dual-energy x-ray absorptiometry measurement were excluded from the analysis.

Adult subjects exposed to H1RA, H2RA, and proton pump inhibitor in NHANES III were identified. H1RA included mepyramine (pyrilamine), antazoline, diphenhydramine, carbinoxamine, clemastine, dimenhydrinate , pheniramine, chlorphenamine (chlorpheniramine), dexchlorphenamine, brompheniramine, triprolidine, hydroxyzine, meclizine, promethazine, cyproheptadine, azatadine, loratadine, mizolastine, terfenadine, levocetirizine, desloratadine, and fexofenadine. H2RA included cimetidine, famotidine, nizatidine, and ranitidine. The only available proton pump inhibitor was omeprazole. Over-the-counter antacid use was determined, although some of these products currently available without a prescription (eg, ranitidine [Zantac, GlaxoSmithKline, Brentford, London, UK]) were available only by prescription at the time of data collection.

Relevant Medication Use

We also considered potentially relevant medications: Glucocorticoids (nasal or oral) may increase risk of osteoporosis, and thiazide diuretics or estrogen could retard bone loss. We did not include osteoporosis therapy such as calcitonin, bisphosphonate, or selective estrogen receptor modulators in the model because few subjects were taking these medications. Medication and supplement information was also collected by asking participants to bring in all currently used products. The identity of each medication was ascertained by asking, "Have you taken or used any medicines for which a doctor's or dentist's prescription is needed in the past month?" Each medication container was checked by the interviewers to record the product name. If the container was unavailable, the interviewer probed for the information. Participants were also asked to describe the health problem for which they took the medicine and how long they had been taking it. The generic name and product code were coded as "blank but applicable" when the name reported did not refer to a specific product or when the name could not be identified.

Covariates

Demographic risk factors (gender, age, and race) and potential covariates for reduced bone mineral density include body mass index (BMI) (kilograms/meter squared), smoking (current vs former or never), alcohol intake (number of drinks in the previous month), poor self-reported health, and history of hip or wrist fracture. Leisure-time physical activity (walking, jogging or running, bicycling or bicycling on an exercise-bike, swimming, aerobics or aerobic dancing, other dancing, calisthenics or exercises, gardening or yard work, and lifting weights) during the previous month was calculated as the metabolic equivalent of the task (MET) per month. History of relevant chronic medical conditions such as arthritis, diabetes, myocardial infarction, congestive heart failure, cerebrovascular accidents, chronic obstructive lung disease (COPD), allergic rhinitis, asthma, and peptic ulcer disease or GERD were based on patients' reports of doctors' diagnoses. Dietary calcium and vitamin D consumption was